Precise PK

Formally known as T. D. M. S. 2000™

Version v0.15.01.22

For Windows

USER MANUAL

Copyright 1986-2015

Healthware, Inc.
Healthware Inc.
7770 Regents Rd 113-632
San Diego, CA 92122
Phone/FAX : (858) 201-6397
e-mail: Information@precisepk.com
www.precisepk.com

The programs and equations contained in Precise PK™ were derived from the medical literature identified in the documentation provided with this program and are combined to provide a system that supplements the judgment of the clinician in dosing various drugs. Precise PK™ is not intended to replace the sound clinical judgment of the user in the care of patients. Neither Healthware, Inc. nor any of its employees shall be liable for any damages resulting from any use of this software package. By the use of this software package, the user waives all warranties, expressed or implied, including any warranties to the accuracy, quality or suitability of Precise PK™ for any particular purpose, either medical or nonmedical.

Healthware, Inc. provides a license to use Precise PK™ under the following conditions:

1. You may make a copy of the program to a working diskette or hard disk as a backup to use on any machine owned by the purchaser, so long as only the number of copies allowed by the Precise PK™ protection scheme is not exceeded.

2. Copies of Precise PK™ screens may be made for teaching or patient care purposes. No copies of Precise PK™ screens may be made for any other purposes, commercial or noncommercial, without written permission of Healthware, Inc.

3. You may not modify, copy or transfer Precise PK™ in any way except as provided for in this license.

Any other uses or copies of Precise PK™ are not allowed under this license, and use of this program indicates users acceptance of these terms and conditions.

The Precise PK™ User Manual is copyright Healthware, Inc, 1986-2015. No part of this Manual may be reproduced in any form or by any means without permission in writing from Healthware, Inc.

Precise PK™ is trademark of Healthware, Inc. and all references to Precise PK™ in this manual refer to the trademark, although they may not be designated as such.

A C K N O W L E D G E M E N T S

The authors would like to thank James Lane, Jr., Pharm.D., William Murray, Pharm.D., Alex Dominguez, Pharm.D. M.A.S., BCPS and Edmund Capparelli, Pharm.D. who have provided numerous pharmacokinetic insights and beta-testing that improved the program.

Abbreviations and Definitions of Terms Used in the PrecisePK™ User's Manual

AUIC	Area under the inhibitory curve (Post / MIC)
BMI	Body mass index
BSA	Body surface error
CLcr	Creatinine clearance
Crs	Serum creatinine in mg/dL
IBW	Ideal body weight
LBW	Lean body weight
MIC	Minimum inhibitory concentration of a bacterium
Peak	The extrapolated serum concentration at the exact end of an IV infusion
Post	The serum concentration at a user-specified time after the end of an IV infusion
TBW	Total body weight

CHAPTER 1. PROGRAM OVERVIEW 6

1.1 WELCOME SCREEN AND MANU BAR 6
1.2 PATIENT & CASE WINDOW 8
1.3 LOAD PATIENT & SEARCH RESULT 11
1.4 MAIN WINDOW 14
1.5 SERUM LEVEL FORECAST & DOSAGE REGIMEN FORECAST 16
1.6 DOSAGE HISTORY & GRAPHICAL ANALYSIS 19
1.7 PRINT REPORT 22
1.8 PROGRAM SETTINGS 23
1.9 USER ACCOUNT 25

CHAPTER 2. PHYSIOLOGIC PARAMETERS 27

BODY SURFACE AREA 27
BODY WEIGHT 27
MODIFIED WEIGHT 27
LEAN BODY WEIGHT 28
DOSING WEIGHT 29
ADJUSTED WEIGHT 29
CREATININE CLEARANCE 29

CHAPTER 3. PHARMACOKINETIC FORMULAS 31

ONE COMPARTMENT 31
Peak Serum Concentration 31
Trough Serum Concentration 31
Average Concentration 31
Loading Dose 32
Dosage Interval 32
Steady-State Levels with First-Order Absorption 33
Concentration at Time t 33
TWO COMPARTMENT 35
Micro-Rate Constants 35
Steady-State Concentration at Time t 35
Nonsteady-State Concentration at Time t 35
MICHAELIS-MENTEN FORMULAS 37
Dosage at Steady-State 37
Concentration at Time t 37
Time to Reach 90% of Steady-State Level 37

CHAPTER 4. DRUG-SPECIFIC PARAMETERS 38

AMINOGLYCOSIDES 38
CIPROFLOXACIN 42
DIGOXIN 44
FLUCYTOSINE 47
LITHIUM 48
LEVOFLOXACIN AND OFLOXACIN 51
PHENOBARBITAL 53
PHENYTOIN 55
PROCAINAMIDE 61

QUINIDINE 63
THEOPHYLLINE 66
VANCOMYCIN 70
APPENDIX A. ANTIBIOTIC PHARMACODYNAMICS 73
APPENDIX B. CURVE FITTING 76

CHAPTER 1. PROGRAM OVERVIEW

1.1 Welcome Screen and Manu Bar

Figure 1.1.1 Welcome Screen and Menu Bar

The Welcome Screen (Figure 1.1.1) displays the program name, version, name of user's institution and the expiration date of the current license. In order to start any calculation, user will need to select or create a patient. There are two choices on the Welcome Screen:

New Patient will lead user to the Patient & Case Window which contains empty patient information.

Load Patient will lead user to the Load Patient Window which allows user to specify the way user want to search for a patient or group of patients in the database.

The **Menu Bar** contains various options that can lead user to almost all pages and windows of Precise PK. User is able to access the Menu Bar in most of the time of using

Precise PK, which allows user to have multi calculation and/or graph windows on the same screen. Here are some brief descriptions of the options.

File:

- **New Patient:** Open a new Patient & Case Window
- **Open Patient:** Open a Load Patient Window
- **Output File:** Outputs a .csv (Comma-Separated Value) file which contains the information of the current patient (Not available until a patient is loaded).
- **Print Report:** Open a Print Report Windows (Not available until a patient is loaded)
- **Log Out:** Log out the current user.
- **Exit:** Exit Precise PK.

Analysis:

- **Dosage Regimen Forecast:** Open a Dosage Regimen Forecast Window (Not available until a patient is loaded).
- **Serum Level Forecast:** Open a Serum Level Forecast Window (Not available until a patient is loaded).
- **Serum Level Analysis:** Open a Dosage History Window (Not available until a patient is loaded).

Settings:

- **Program Setting:** Open a Program Setting Window which allows user to change the setting of Precise PK (Available settings may vary depends on the Login Role).
- **Manage User Account/Update User Information:** Open a User Management Window (Administrator) or a Profile Window (Normal User) which allows user to either manage all users' account or update the information of current user.

Help:

- **About:** Open the Precise PK Information Page.
- **Software Update:** Open the Software update Page which allows user to check and download the latest version of Precise PK.
- **Manual:** Open the Manual Window which contains an abstract version of the Precise PK User Manual for simple reference.

1.2 Patient & Case Window

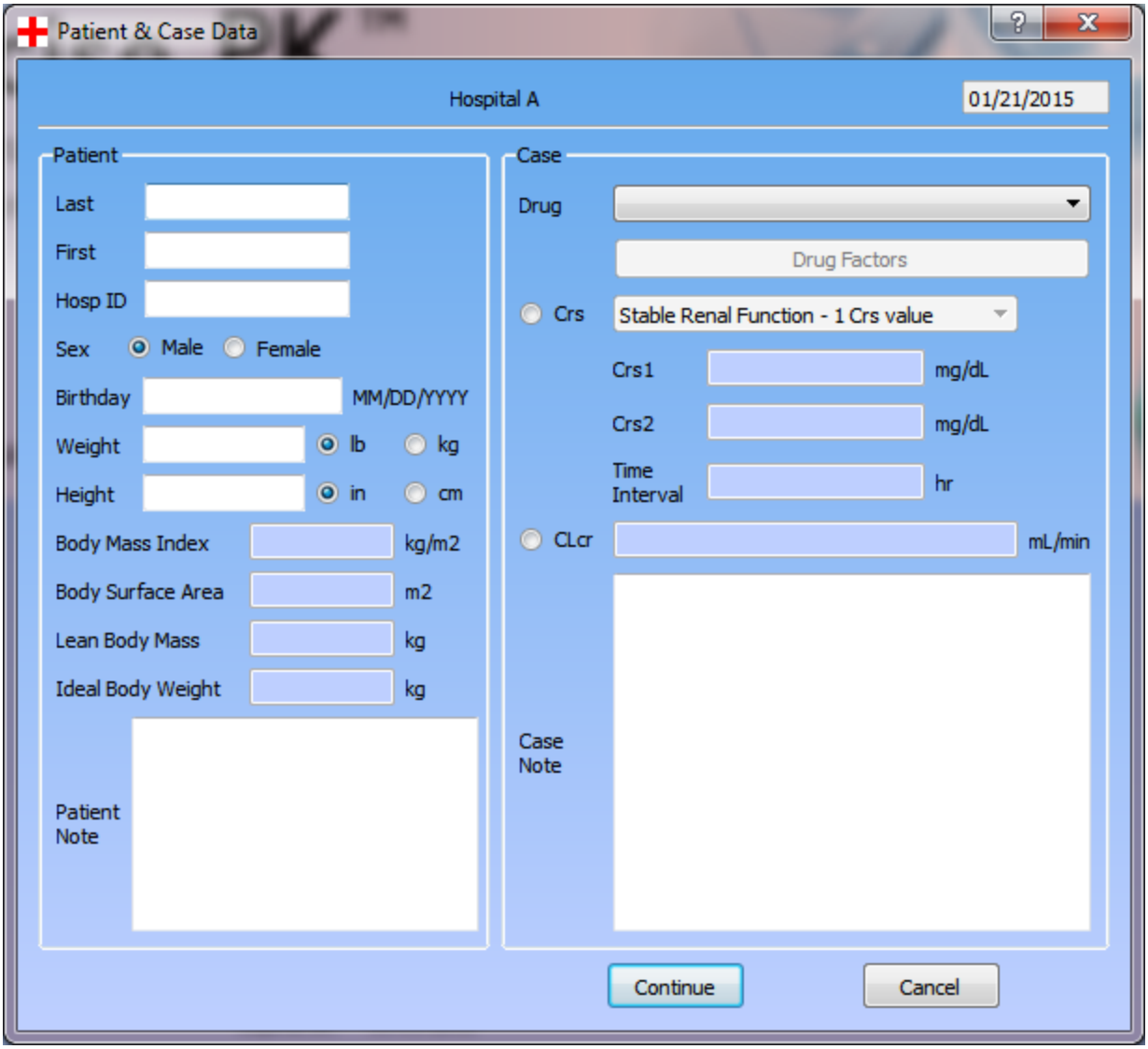

Figure 1.2.1 Patient & Case Window

After selecting a specific patient's case or a new patient, user will be lead to the Patient & Case Window (Figure 1.2.1).

This screen is used to gather information about the patient and drug of interest. In the first three fields of the left **(Patient)** column, user may enter the patient's **Last** and **First** names and any **Hospital Identification** number. These fields are used to store and later identify the patient in the database. User may jump between fields with a mouse click or tab key.

Birthday is entered as mm/dd/yyyy.

Sex is entered by clicking on the appropriate radio button, Male or Female.

Weight and **Height** are entered as numbers and the correct units are selected using the buttons to the right of each box. These fields' default unit can be set in Program Setting Window. The patient's total body weight should always be entered. Precise PK will make the proper adjustments to the weight for subsequent calculations. Entering the adjusted weight here may result in erroneous calculations. After the Sex, Birthday, Weight and Height fields are entered; the calculated Body Mass Index, Body Surface Area, Learn Body Mass and Ideal Body Weight will appear in the left column.

Patient Note will be stored with the Patient record in the database. Information in this field will be retrieved whenever the Patient or any of the patient's Case records are retrieved.

In the right **(Case)** column user enters data about the particular course of drug therapy that user is studying.
Drug is selected from the drop-down menu. User may also type in the **first letter** of the drug name and the drop down menu will display the drug as soon as a match occurs.

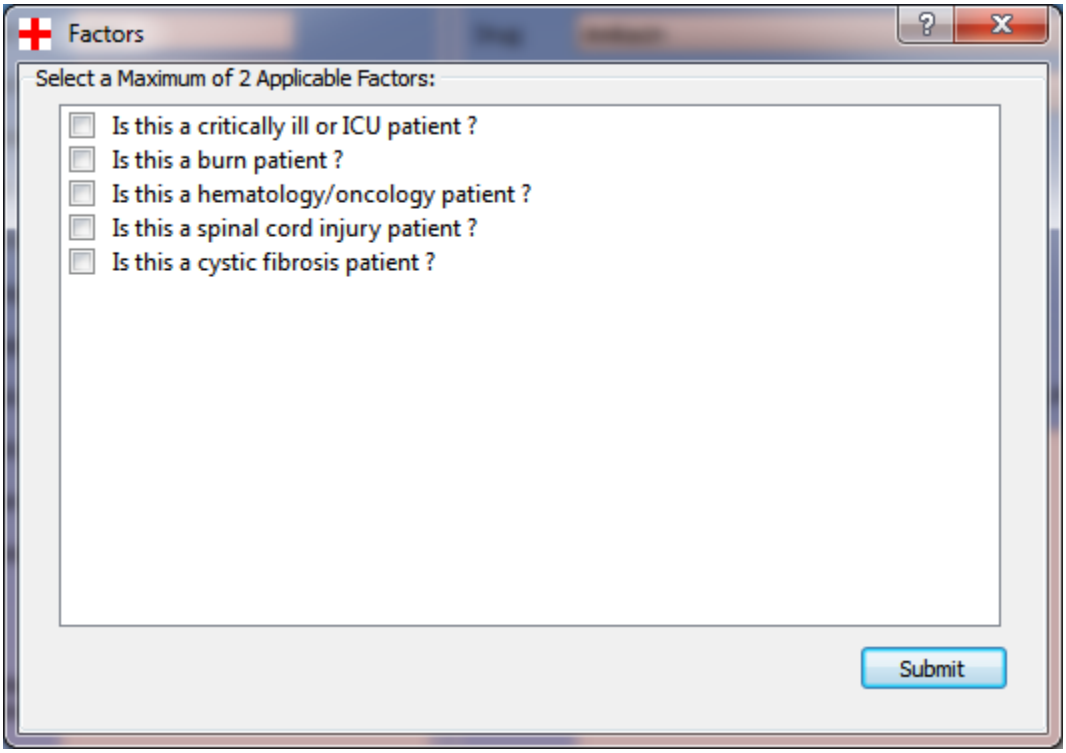
Factors
Select a Maximum of 2 Applicable Factors:
Is this a critically ill or ICU patient ?
Is this a burn patient ?
Is this a hematology/oncology patient ?
Is this a spinal cord injury patient ?
Is this a cystic fibrosis patient ?
Submit

Figure 1.2.2 Drug Factors

A Factor Window (Figure 1.2.2) will appear if user clicks the Drug Factors Button after finishing filling or selecting the **Birthday** and **Drug**. User can enter up to two factors

known to affect the pharmacokinetics (by at least 10%) of the drug being used in this case. Click on the check box to the left of any factor(s) that are applicable. Once the appropriate factors have been checked, click the **Submit** button at the bottom of the window and user will see the selected factors appearing on the right of the Patient & Case Window.

The patient's creatinine clearance (CLcr) can be calculated from serum creatinine (Crs) or it can be entered directly if user has a measured value. Select either **Crs** or **CLcr** with the radio button and enter the value in the corresponding units in the box to the right of user's selection.
Also, Precise PK provides two options of Crs renal function. User can choose either one of them by selecting the Crs radio button, make the selection of which renal function that user would like to use, and then input the corresponding Crs values and/or Time Interval in the proper fields.

Serum **Albumin** is only required when user have selected the drug phenytoin. Otherwise, this entry is skipped. To fit unbound phenytoin levels, enter 0.01 as the serum albumin concentration.

The date that this particular Case was updated is displayed on the top of the right column

Case Note will be stored with the Case record in the database. Information in this field will be retrieved whenever this Case record is retrieved.

The **Cancel** button at the bottom of this screen allows user to go back to the previous screen and discard all changes user have made for this patient or case. The **Continue** button will proceed with analysis of this case.

1.3 Load Patient & Search Result

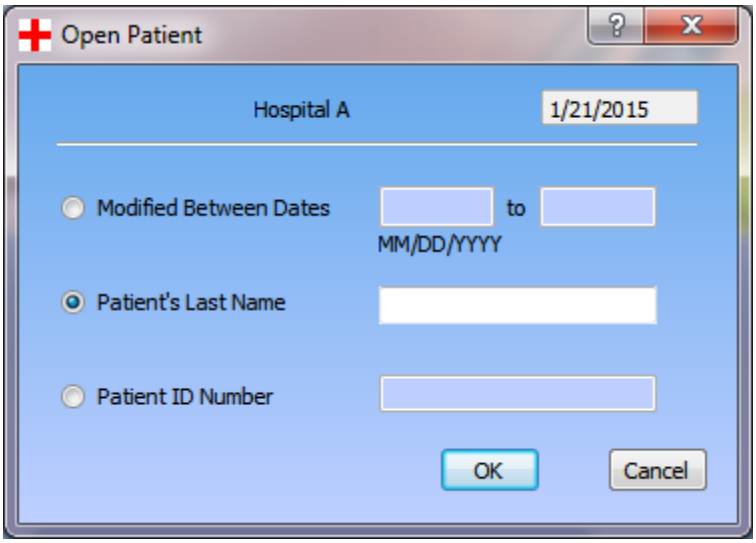

Figure 1.3.1 Drug Factors

If user selects **Load Patient** in the Welcome Window or in the Menu Bar, user will see the Open Patient Window (Figure 1.3.1). This screen allows user to search for a patient or group of patients in the database. User can choose one of the following ways to filter the search result by clicking the radio button.

Modified Between Dates Selecting start and end dates in the boxes of this screen will search user's entire database to identify patient records that have not been modified since this time period. Records from this time period that have been updated since the end of the time period are *not* included.

Patient's Last Name allows user to search for a patient by the last name. Partial name searches are possible, so entering the letter "An" will retrieve all patients' whose last name starts with "An". User can also type in an empty Last Name which will then display all patients in the database.

Enter Patient ID Number allows user to search by the identification number user have stored in the database, such as the patient's medical record number.

The **Cancel** button will lead user back to the pervious screen and cancel the search operation. The **OK** button will lead user to the Search Result Window(Figure 1.3.2) which displays the result of user's search.

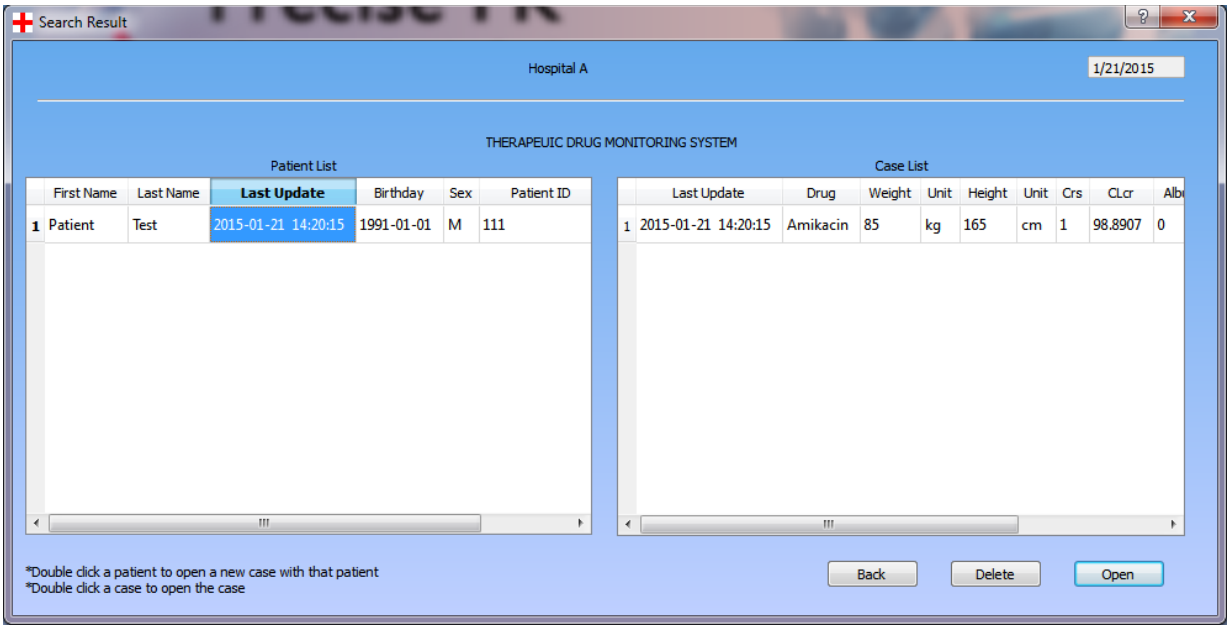

Figure 1.3.2 Search Result

The Search Result Window (Figure 1.3.2) will display the patient records which fits users search filter and it will displays the record on the left area. If no record fits the filter or there is no patient in the database then the area will be empty.

In this screen, there are some operations user could choose to obtain different results.

Double click a Patient on the left will open a Patient & Case Window with the patient information.
Single click a Patient on the left will show all the cases of that specific patient on the right area. Also it will put that patient or case in the "selected" status.
Double click a Case on the right will open a Patient & Case Window with the patient information and the case information.

Single click a Case on the right will put that case in the "selected" status.

On the bottom of the screen there are three buttons. The **Back** button will lead user back to the Load Patient screen which user can reset the search filter and search again. The other two buttons' behavior will be different depends on the "selected" status of the patient on the left area and the case on right area:

The **Delete** button will delete the corresponding patient or case record which is under the "selected" status. If user decides to delete a case, just single click a case then click the delete button. The selected case will then be removing from the database. If user decides to delete a patient, just single click a patient then click the delete button. Note that deleting a patient will also *delete all the cases of that patient.*

The **Open** button behaves the same as the double click operation. Selecting a patient and click **Open** will open a Patient & Case Window with the patient information; similarly, selecting a case and click **Open** will open a Patient & Case Window with the patient information and the case information.

1.4 Main Window

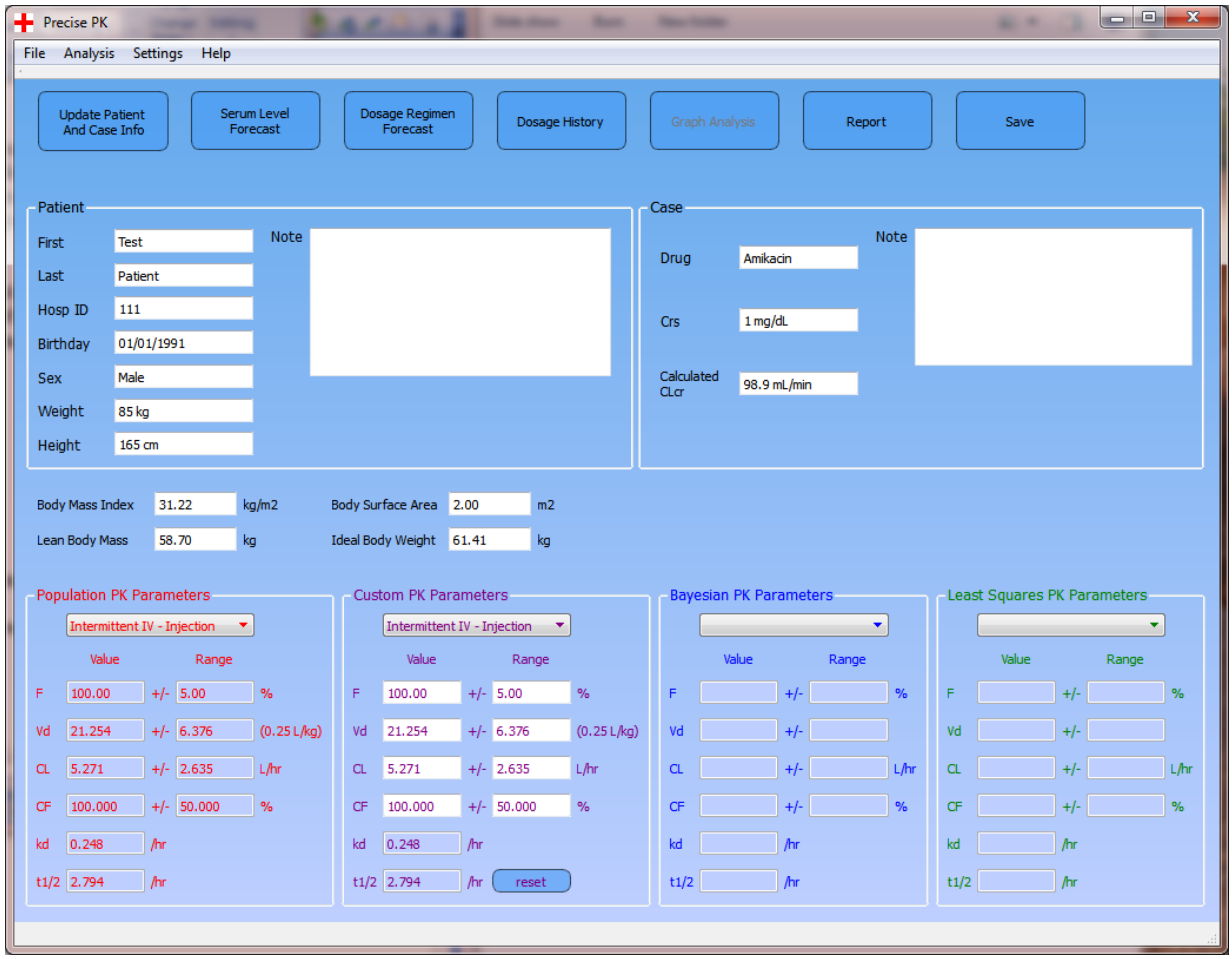

Figure 1.4.1 Main Window

Once user click continue from the Patient & Case Window, user will be lead to the Main Window (Figure 1.4.1), which can be considered as the central panel of Precise PK. The Main Window contains rich information related to patient and case; also it is the place where user can see all the PK parameters. Moreover, user navigates at difference places from the Main Window.

The Main Window can be separated by three main areas:

On the top of the Main Window is group of buttons.

- **Update Patient And Case Info** will open the Patient & Case Window which can allow user to update or change the patient or case information. Note that once the patient has been saved or the case is loaded from database, some values of patient and case are not changeable.
- **Serum Level Forecast** will open a Serum Level Forecast Window.
- **Dosage Regimen Forecast** will open a Dosage Regimen Forecast Window.

- **Dosage History** will open the Dosage History Window.
- **Graph Analysis** will open the Graph Analysis Window. Note that it is not available until user has entered the dosage history.
- **Report** will open the Print Report Window.
- **Save** will save the current patient and case information into the database. It will not be available if there is no change after the last save operation.

In the middle of the Main Window displays the information about the patient and the case. If user want to change any of them user can click the **Update Patient And Case Info** on the top.

At the bottom of the Main Window there four sets of PK parameters. User can choose different routes in different set to show the corresponding parameters. The **Population PK Parameters** cannot be change. However, user can use another set of parameters called "**Custom PK Parameters**" to compute different numbers. The other two sets of PK parameters, **Bayesian PK parameters** and **Least Squares PK Parameters** will be available once enough number of dosage history and serum level have been entered and analysis.

The **Reset** button under the set of **Custom PK Parameters** will resets all the customized PK parameters back to the **last saved version**. By default, if there no customized PK parameters are set for the patient, and then the **Custom PK Parameters** will be the same as **Population PK Parameters.**

1.5 Serum Level Forecast & Dosage Regimen Forecast

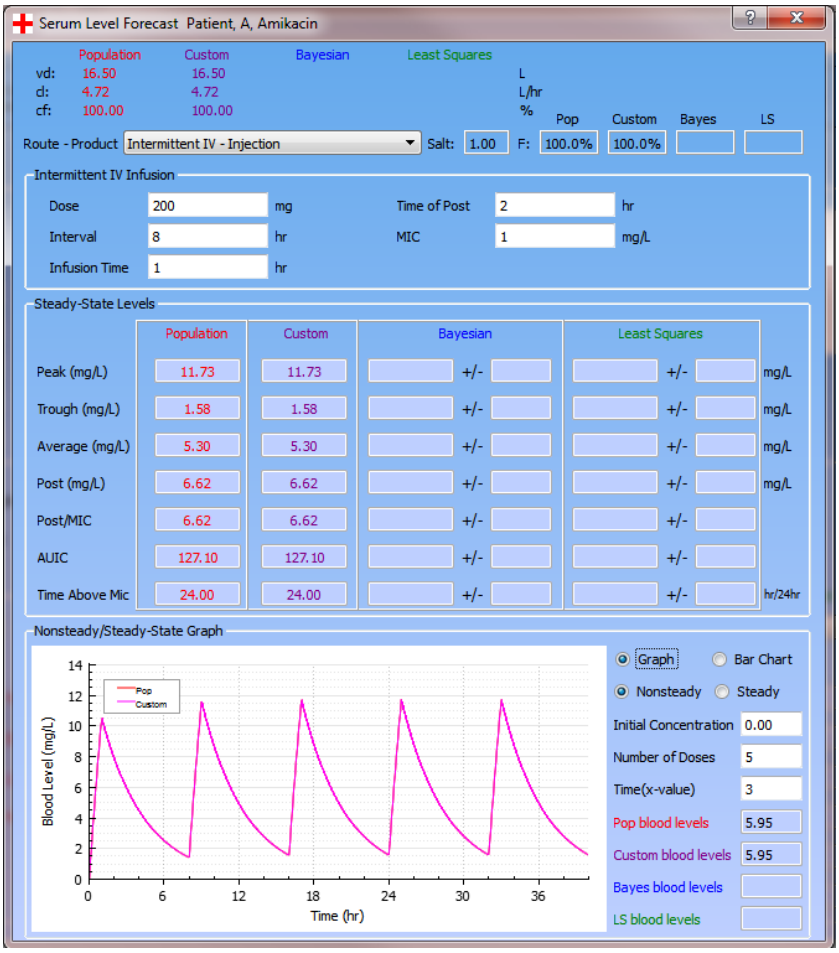

Figure 1.5.1 Serum Level Forecast Window

This Serum Level Forecast Window (Figure 1.5.1) allows user to predict the serum drug concentrations achieved by dosage regimen that user enter. Results are calculated using all four types of pharmacokinetic values if available. When user modified the **Custom PK Parameters** on the Main Window, the corresponding values are also changed automatically.

User can select route and specific drug product from the drop-down box on top of the screen. Different route might have different user interface for entering the dosage regimen. For intermittent administration, enter the dosage regimen that user desire and the steady-state serum levels predicted to be produced by this regimen are displayed. For administration by continuous infusion, simply enter the desired serum and the program will calculate the infusion rate needed to achieve this concentration. For antimicrobial agents, enter the minimum inhibitory concentration (MIC) of the organism to calculate pharmacodynamics values (Post/MIC, Time Above MIC and AUIC) at steady-state

which are displayed at the bottom of the second column.

The bottom screen provides the graph using the entered dosage regimen. The graph will originally start at concentration 0 and then simulate how this dosage regimen gets to the steady-state. Bar chart will provide a comparison between different PK for each value we calculate. User can click on the legend of the graph to hide or show the corresponding set of value. (For example, if I want to hide population graph, just click on the Pop in the legend.) User can also set an initial concentration instead of using 0 by default and can also specify how many intervals (doses) the graph should draw. By entering Time (x-value), it will automatically show the corresponding level (y-value) for each PK parameters.

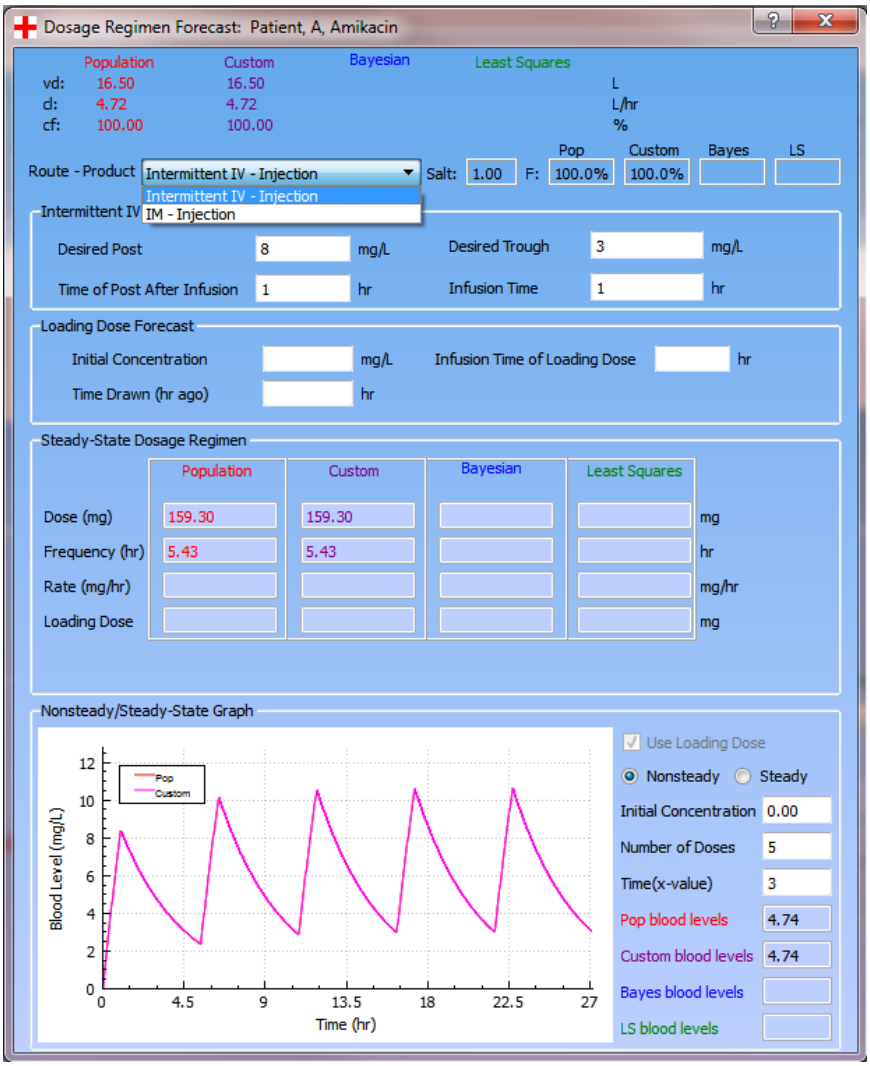

Figure 1.5.2 Dosage Regimen Forecast Window

This Serum Level Forecast Window (Figure 1.5.2) allows user to predict the dosage regimen required to achieve the exact serum drug concentrations that user enter. Results are calculated using all four types of pharmacokinetic values if available. When user modified the **Custom PK Parameters** on the Main Window, the corresponding values are also changed automatically.

User can select route and specific drug product from the drop-down box on top of the screen. Different route might have different user interface for entering the desired serum concentration. After entering the desired serum concentrations and times, the exact dosage regimen required to produce the serum drug concentrations user specify are displayed in the Steady-State Dosage Regimen box. User may enter further information in the Loading Dose Forecast box. If the patient has been on the drug and user have a serum concentration drawn at a known time, user can enter these and the program will calculate the dosage required to produce the desired level that user specified after the first dose. Because calculations often result in impractical doses or frequencies, the results obtained on this screen should be considered approximate dosage regimens.

The bottom screen provides the graph using the calculated dosage regimen. The graph will originally start at concentration 0 and then simulate how this dosage regimen gets to the steady-state. Bar chart will provide a comparison between different PK for each value we calculate. User can click on the legend of the graph to hide or show the corresponding set of value. (For example, if I want to hide population graph, just click on the Pop in the legend.) User can also set an initial concentration instead of using 0 by default and can also specify how many intervals (doses) the graph should draw. By entering Time (x-value), it will automatically show the corresponding level (y-value) for each PK parameters.

1.6 Dosage History & Graphical Analysis

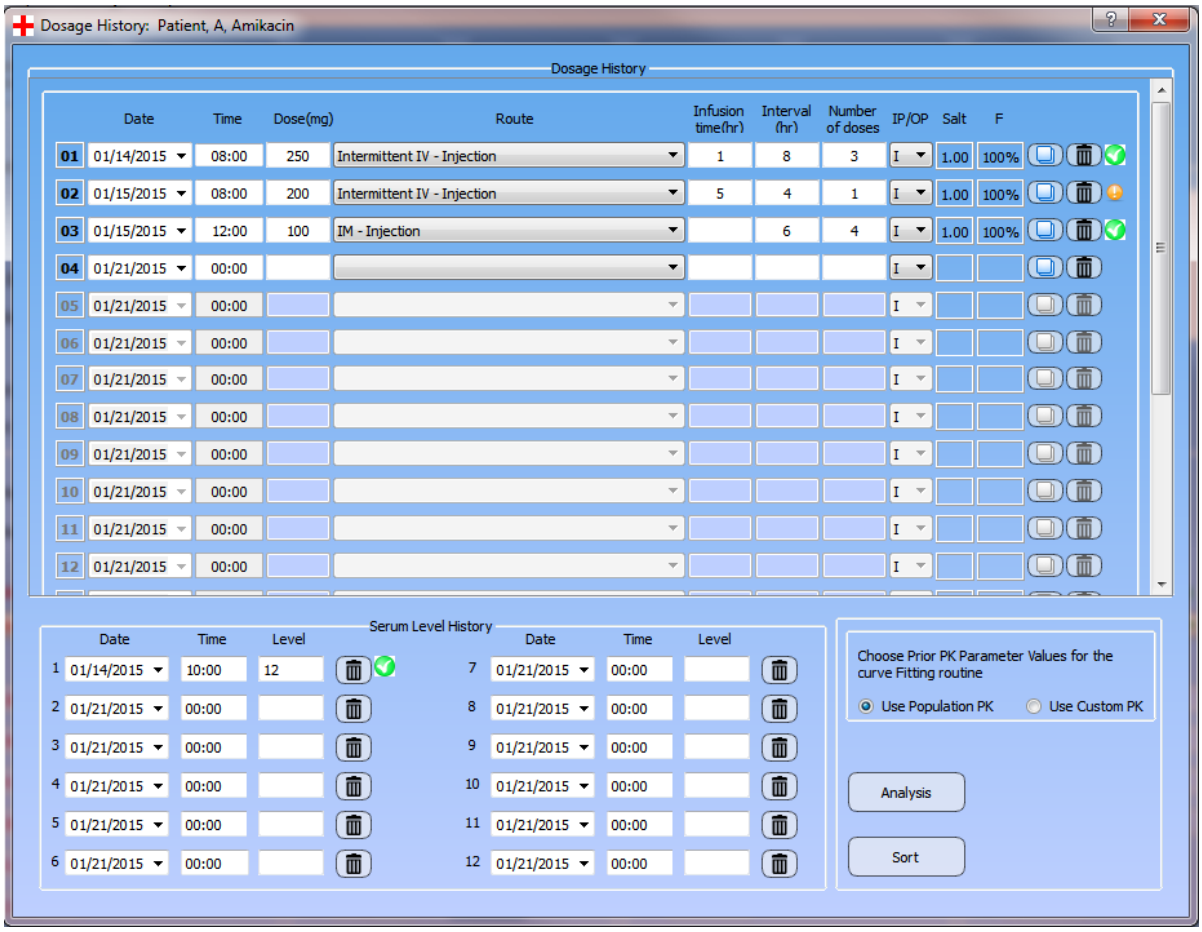

Figure 1.6.1 Dosage History Window

This Dosage History Window (Figure 1.6.1) allows user to enter the dosage history and serum level history for this case.

In Dosage History Window, user should enter all the necessary information. Routes are selected by the drop-down menu. For IV route, user need to enter all the information and for other route, infusion time can be omitted. If a row is completed, a green check sign will appear on the right side. If the completed row shows some strange behavior, the green check sign will become a yellow warning sign that indicates there MIGHT be something wrong, but the program can still do the calculation. (i.e. in this case, infusion time is greater than interval.) There are two buttons at the end of each row. The first one is **Copy** button, and it will copy the previous row's value into the current row. The second one is a **Delete** button, and it will delete the value in the current row and restore it to default value.

In Serum Level History, user will enter the measured level that the specific time. A green

check will also appear if the row is complete and a yellow warning sign will appear if the row is complete but shows some strange behavior. (i.e. level is measured during infusion.)

User can select which set of PK parameters is used in the analysis and curve fitting by selecting the radio buttons on the lower right corner. Program will call the selected set as **Prior PK Parameters.**

Warning: If there are multiple Non-IV F values, program will used the most recent selected route's F value as the based value for curve fitting. As a result, the analysis might not be very accurate.

Analysis will lead user to the graphical analysis screen. Data entered in this screen will be transferred and used in the analysis.

Sort will sort the complete row in increasing time order. Warning: All incomplete rows will be erased.

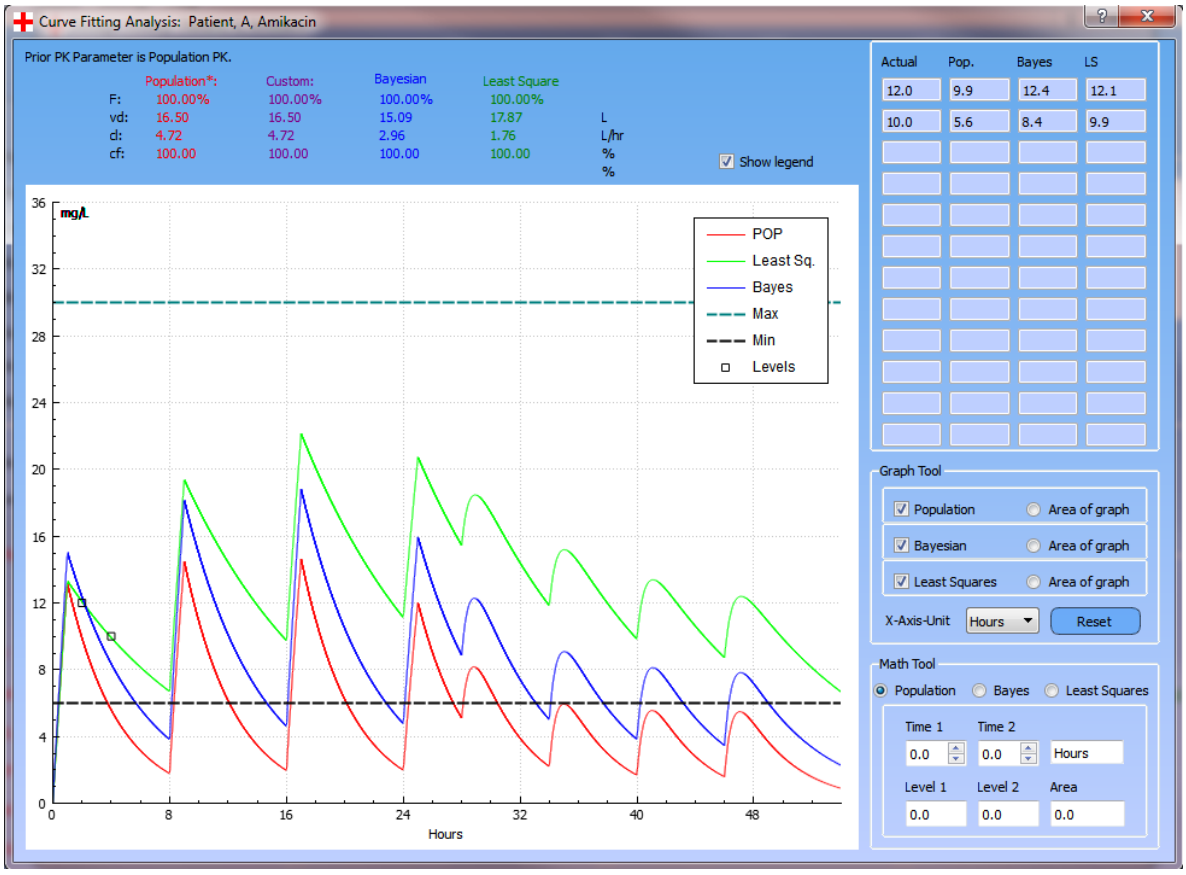

Figure 1.6.2 Graphical Analysis Window (also called Curve Fitting Analysis)

The Graphical Analysis Window (Figure 1.6.2) will display the result of curve fitting. Entered levels are displayed as small rectangles on the graph. Each set of PK is represented by its own color.

On the upper left corner, program will explicitly tell the user which set of PK parameters is used. The table on the upper right corner shows the serum level history and its fitted value using fitted parameters. On the lower right corner, user can select which set of values to be showed on the graph in the Graph Tool box. In addition, by clicking the Area of graph radio button, it will highlight the area clearly on the graph. User can also select the unit for x-axis using the drop-down menu in the Graph Tool box. The **reset** button will reset everything and restore the screen to default state. The program can also calculate the area of the graph by entering Time1 and Time2 in the Math Tool box.

By clicking the "**Show Legend**" check box, it will show or hide the graph legend based on the checkbox status.

Reset will reset the screen to default state.

1.7 Print Report

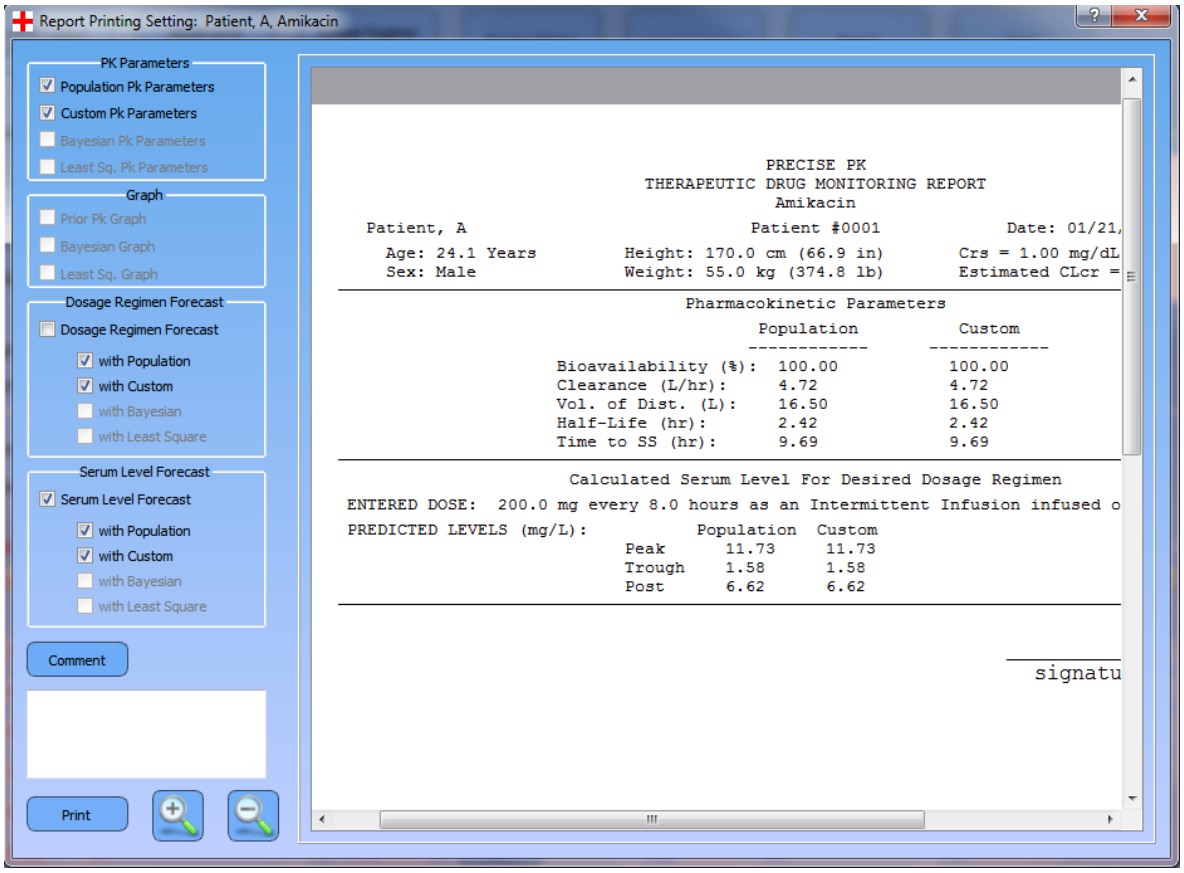

Figure 1.7.1 Print Report Window

The Print Report Window displays what the report looks like in real time. User can select what content to be printed on the report and the preview of the report will update automatically based on what user selects. By default, all available selections are selected automatically. User can change the default select on the program setting page. (i.e. don't select **Least Square PK Parameters** automatically.)

When user needs to enter comment, user can press the **Comment** button at the bottom left. This will pop up a text area for user to enter comments. There are also zoom-in and zoom-out buttons, represented by magnifier with the plus and minus signs. Press the print button will direct user to the printer setting page that allow user to print the report.

Comment will pop up a window that allow user to enter comment.

Print will lead user to the printer setting page that allow user to print the report.

1.8 Program Settings

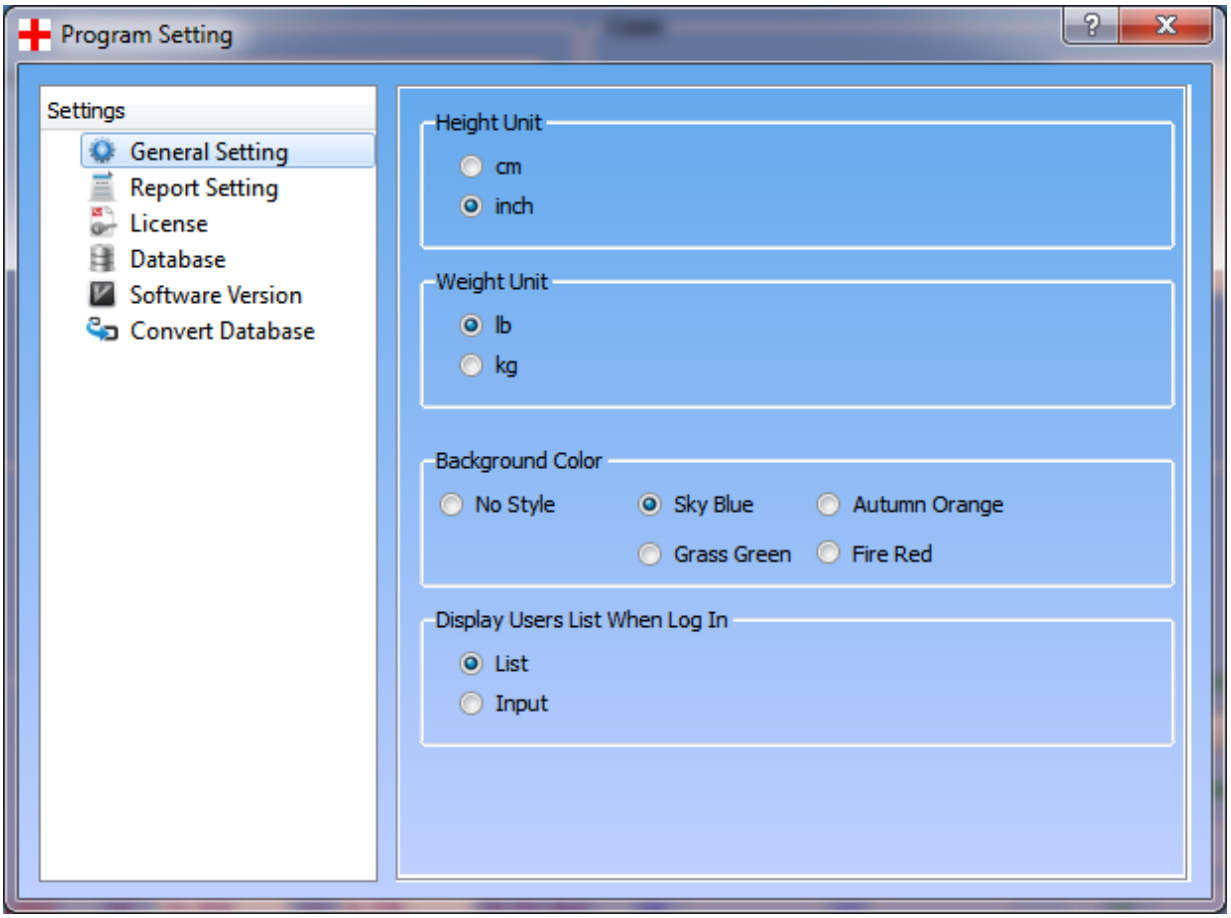

Figure 1.8.1 Program Setting Window

The Program Setting Window (Figure 1.8.1) is the place where user can change the setting of Precise PK. The window contains different pages and each one of them handles one area of the setting. User can switch between different pages using the menu panel on the left side.

- **General Setting**
  - **Height Unit** and **Weight Unit** set the default units for new Patient.
  - **Background Color** sets the color style of the program.
  - **Display Users List When Log In** options changes the Log In Window setting when user log in.
- **Report Setting** This page sets the default values for report printing.
- **License** In this page, user can set the path of the license file or update license.
- **Database** This page shows the current path of the database and which user makes the last modification. User can change the path of the database by clicking

Change button. Note that all Precise PK database are associated with a Precise PK license, which means the change database operation might failed because the license is not match.

- **Software Update** This page allows user to check and update to latest version of Precise PK.
- **Convert Database** This page allows user to convert or import a Precise PK database to a Precise PK database.

1.9 User Account

Precise PK have four types of users, each one of them have different levels of authorization and limitation.

User Type	Limitation
Demo	• No access to database • Fixed Patient name • Allow drug: Vancomycin, Theophyline, Gentamicin • Can only see the page of User Choice Drug, but cannot summit. • Can update license
Guest	• No access to license • Cannot read/write database • Can change database path
Normal User	• Cannot add/delete user • Can only change current user's info • Can update license • Can access to database
Administrator	• No limitation

User Accounts are created or managed in User Account Manage Window.

By default, Precise PK will be under Demo Mode, which all users are Demo users when one but not only one of the following situation occurs:

- New download
- License file is not found
- License is expired
- Unknown errors occurs

Once user have registered a valid license and configure the database correctly, a default Administrator will be created with following information:

- ID: 1
- User name: admin
- Name: admin
- User type: administrator
- Password: no password

If there is more than one user (Normal User or Administrator) or the only one user has set up the password, then a Log In Window (Figure 1.9.1) will appear every time Precise PK starts.

Figure 1.9.1 Log In Window

User can select the user name and input the password (if no password then this step can be skipping) then clicks Log In. If user selected the "Input" option in Program Setting, then the exact user name need to be entered. After the log in user can use Precise PK as either a Normal User or Administrator depends on the user's role.

User can also choose the click **Guest** button to use Precise PK as a Guest User. Guest User has some restriction. However no user name or password is required for Guest user. Note that some database errors, such as failing to connect the database, may cause user to be logged in as Guest User.

CHAPTER 2. PHYSIOLOGIC PARAMETERS

This chapter provides documentation of the formulas and methods used to estimate various physiologic parameters of the patient. These, in turn, are used to estimate the pharmacokinetic parameters used in dosage regimen and serum level forecasts as well as starting points for the curve fitting routines.

Body Surface Area

The body surface area (BSA) is calculated by the formula of Haycock GB et al. J Pediatr 1978;93:62-6.
Formula:

$$BSA = weight^{0.5378} \times height^{0.3964} \times 0.024265$$

where BSA is in M^2, weight is in kg and height is in cm.

Body Weight

The patient's total body weight is entered in the Patient Demographic screen. Precise PK™ will calculate the appropriate weight to use for the various calculations used in the program.

Modified Weight

The modified weight of adults over 18 years of age is defined in Precise PK™ as the ideal body weight (Devine BJ. Drug Intell Clin Pharm 1974;8:650-5) if the patient's actual weight is greater than or equal to the ideal body weight, but less than the lean body weight. For morbidly obese patients whose lean body weight is greater than the ideal body weight, the modified weight equals the lean body weight. For patients less than their ideal body weight, modified weight equals the actual (total) body weight.

The modified weight of children aged 1 to 16 years is defined as the ideal body weight (Traub SL, Kitchen L. Am J Hosp Pharm 1983;40:107-10 and Traub SL, Johnson CE. Am J Hosp Pharm 1980;37:195-201.) if the actual weight exceeds 1.2 times the ideal body weight, otherwise the modified weight is the total body weight. In adolescents aged 16 to 18 years of age who are over 5 ft, the modified weight is the average of the ideal body weights calculated by the adult and pediatric formulas. In infants under the age of 1 year, the modified weight is the total body weight.

Formula for IBW in kg:

Adults over 18:

$$IBW\ (males) = 50.0 + 2.3\ \times (height\ in\ inches - 60)$$

$$IBW\ (males) = 45.5 + 2.3\ \times (height\ in\ inches - 60)$$

Children 18 or under:

height under 5 ft.:

$$IBW\ in\ kg = 2.396\ \times\ e^{0.01863\ \times height\ in\ cm}$$

height 5 ft or over:

$$IBW\ in\ kg\ (male) = 39.0 + 2.27\ \times\ \text{height in inches over 5 ft.}$$

$$IBW\ in\ kg\ (female) = 42.2 + 2.27\ \times\ \text{height in inches over 5 ft.}$$

Lean Body Weight

Lean body weight (LBW) is defined as the weight of the body minus the weight of body fat.(Han PY et al. Clin Pharmacol Ther 2007;82:505-8.) This is in contrast to ideal body weight which includes a normal amount of body fat weight.

LBW Formulas:

$$LBW(males)\ =\ \frac{9270\ *\ \text{total body weight (kg)}}{6680\ +\ (216\ *\ \text{BMI})}$$

$$LBW(females) = \frac{9270\ *\ \text{total body weight (kg)}}{8780\ +\ (244\ *\ \text{BMI})}$$

Where

$$BMI(body\ mass\ index)\ =\ \frac{\text{total body weight (in kg)}}{\text{height}^2\ (\text{in m}^2)}$$

Dosing Weight

A dosing weight is used for some calculations. Dosing weight is defined as follows: For patients at or below their IBW:

$$Dosing\ weight = total\ body\ weight$$For patients above their IBW:

$$Dosing\ weight = IBW + 0.4\ \times (total\ body\ weight - IBW)$$

Adjusted Weight

An adjusted weight is used for some calculations, based on literature documentation. Adjusted weight is defined as follows:

For patients at or below their IBW:

$$Adjusted\ weight = total\ body\ weight$$

For patients above their IBW, but less than their LBW:

$$Adjusted\ weight = IBW$$

For patients in whom LBW > IBW:

$$Adjusted\ weight = LBW$$

Creatinine Clearance

The creatinine clearance (CLcr) calculation used depends on the age of the patient. One of two formulas is used. In patients 18 years of age or older, the method of Cockroft and Gault (Nephron 1976;16:31-41). The adjusted weight (defined above) is used in the calculations. Ideal body weight (IBW) is used because it is a simple and widely accepted measurement with relatively good predictive ability (Rosborough TK et al Pharmacotherapy 2005;25:823-
30). In morbid obesity, when LBW > IBW, LBW is used in the equation because it has better predictive value (Demirovic JA et al. Am J Health Syst Pharm. 2009;66:642-8). In children from age 0.5 years to 18 years the method of Traub and Johnson (Traub SL and Johnson CE. Am J Hosp Pharm 1980;37:195-201) is used. In children less than 0.5 years of age, no calculation is made.

Formulas:

Adults over 18:

$$CLcr\ (males) = \frac{(140 - age) \times adjusted\ weight}{72\ \times Scr}$$

$$CLcr\ (males) = \ 0.85\ \times above\ value$$

where CLcr is in mL/min, weight is in kg, and Crs is in mg/dL

Children 18 or Under:

$$CLcr\ (mL/min/1.73M^2) = \ 0.48\ \times \frac{height}{Crs}$$

This value is then multiplied by the child's BSA/1.73 to obtain the individual's CLcr value

where height is in cm and Crs is in mg/dL.

As a final check, CLcr is not allowed to go above 90 mL/min/m^2 in patients 5 or more years of age, or over 58 mL/min/m^2 in patients under 5 years of age. These values are approximately 2 standard deviations above the mean in populations with normal renal function.

CHAPTER 3. PHARMACOKINETIC FORMULAS

This chapter provides the user with the equations used to calculate various serum level and dosage regimen data throughout the program.

ONE COMPARTMENT

Peak Serum Concentration

This equation calculates the steady-state peak serum concentration for intravenously administered drugs that results from infusing a dose (D) over time (t_{inf}) with a dosage interval
(τ), a starting concentration (cp), a Clearance (CL) and a volume of distribution (Vd).
Formula:

$$Peak_{ss} = \frac{S \times F \times K_0 \times (1 - e^{-Kd \times t_{inf}})}{CL \times (1 - e^{-Kd \times \tau})}$$

where K_0 = dose/t and Kd = CL/Vd.

Trough Serum Concentration

This formula calculates the minimum serum concentration at steady-state during an intravenous dosage regimen with a dosage interval of τ.

Formula:

$$Trough_{ss} = Peak_{ss} \times e^{-Kd \times (\tau - t_{inf})}$$

where Kd = CL/Vd and t_{inf} is the infusion time.

Average Concentration

This equation is used to calculate the average steady-state serum concentration with all routes of administration.

Formula:

$$Avg_{ss} = \frac{S \times F \times K_0}{CL}$$

where K_0 is either the infusion rate or the daily dosage as appropriate.

Loading Dose

This formula calculates the loading dose needed to achieve a specified peak of an intravenous drug infused over time (t) given clearance (CL), initial serum concentration (cp), volume of distribution (Vd), salt fraction (S) and bioavailability (F).

Formula:

$$Loading\ dose = \frac{CL \times t \times [peak - (cp \times\ e^{-Kd \times t})]}{S \times F \times (1 - e^{-Kd \times t})}$$

where Kd = CL/Vd and t is the duration of the infusion with IV dosage or time to peak after a single dose with PO and IM administration.

Dosage Interval

This formula calculates the dosage interval needed to achieve a desired trough given a desired peak, an elimination rate constant of Kd and an infusion time of t.

Formula:

$$Interval = t + \frac{\ln\,(peak/trough)}{Kd}$$

where t is the infusion time with IV doses, and the time to peak at steady-state for IM and oral doses.

Time to Peak - Single Dose

This formula calculates the time of the peak serum concentration following a single dose of a drug given PO or IM with an absorption rate constant of Ka and an elimination rate constant of Kd. This time is used in the above formulas to approximate an "infusion time (t)" for IM and oral doses.

Formula:

$$T_{peak} = \frac{\ln\,(Ka/Kd)}{Ka - kd}$$

where Ka is the absorption rate constant and Kd is CL/Vd.Dosage Requirement

These formulas calculate the dose required to achieve a desired peak given a clearance (CL), volume of distribution (Vd), salt fraction (S), bioavailability (F), and dosage interval (J).

IV Formula:

$$Dosage = \frac{peak \times CL \times t \times (1 - e^{-Kd \times \tau})}{S \times (1 - e^{-Kd \times t_{inf}})}$$

where Kd = CL/Vd and t_{inf} is the infusion time.

PO/IM Formula:

$$Dosage = \frac{peak \times Vd \times (1 - e^{-Kd \times \tau})}{F \times S \times e^{-Kd \times TMax_{ss}}}$$

where Kd = CL/Vd and $TMax_{ss}$ is the time to peak at steady-state as calculated below under Steady-State Levels With First-Order Absorption.

Steady-State Levels with First-Order Absorption

These equations calculate the steady-state peak ($Peak_{ss}$) and trough ($Trough_{ss}$) concentrations for orally and intramuscularly administered doses (D) of drugs with a bioavailability fraction (F), salt fraction (S), volume of distribution (Vd) and absorption and elimination rate constants (Ka & Kd, respectively) at a given dosage interval (τ). The time to peak at
steady-state ($TMax_{ss}$) is calculated as an intermediate step for calculating $Peak_{ss}$

Formulas:

$$Peak_{ss} = \frac{S \times F \times D}{Vd} \times \frac{e^{-Kd \times TMax_{ss}}}{1 - e^{-Kd \times \tau}}$$

$$Avg_{ss} = \frac{S \times F \times D}{CL \times \tau}$$

$$TMax_{ss} = \frac{\ln\left(\frac{Ka \times (1 - e^{-Kd \times \tau})}{Kd \times (1 - e^{-Ka \times \tau})}\right)}{Ka - Kd}$$

$$Trough_{ss} = \frac{S \times F \times D \times Ka}{Vd \times (Ka - Kd)} \times \left(\frac{e^{-Kd \times \tau}}{1 - e^{-Kd \times \tau}} - \frac{e^{-Ka \times \tau}}{1 - e^{-Ka \times \tau}}\right)$$

Concentration at Time t

These equations are used to calculate the serum concentration (cp) at a given time (t) after a dose where S is the salt fraction, D is the dose, CF is the compliance factor, F is the bioavailability, K_0 is the infusion rate, t_{inf} is the infusion time, Vd is the volume of distribution, CL is the clearance and Kd is CL/Vd. They are used in both the curve fitting routines and in the graphics calculations. The concentration during a multiple dose regimen is calculated by superposition (i.e., addition of the contributions of all prior doses). The superposition method is used in both the curve fitting and graphics portions of Precise PK™ to determine the serum concentration at times of interest.

IV Formulas:

IV Bolus:

$$Cp_t = \frac{CF \times S \times D}{Vd} \times e^{-Kd \times t}$$

During IV Infusion:

$$Cp_t = \frac{CF \times S \times K_0}{CL} \times (1 - e^{-Kd \times t})$$

After the End of An Infusion:

$$Cp_t = \frac{CF \times S \times K_0}{CL} \times (1 - e^{-Kd \times t_{inf}}) \times e^{-Kd \times (t - t_{inf})}$$

PO/IM Dosage:

$$Cp_t = \frac{CF \times S \times F \times Ka \times dose}{Vd \times (Ka - Kd)} \times (e^{-Kd \times t} - e^{-Ka \times t})$$

TWO COMPARTMENT

Micro-Rate Constants

The following equations are used to calculate micro-rate constants after establishment of clearance (CL), total volume of distribution ($Vd_ß$), volume of distribution of the central compartment (Vc) and the transfer rate constant between the peripheral and central compartments (K_{21}) by population estimates.

Formulas:

$$K_{10} = CL/Vc$$

$$\beta = CL/Vd_\beta$$

$$\alpha = K_{21} \times K_{10}/\beta$$

Steady-State Concentration at Time t

This equation is used to predict the serum concentration at steady-state (Cp_{ss}) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of K_o over an infusion time of (t_{inf}) and at a dosage interval of (τ). During the infusion, t_{inf} and t are equal.

Formulas:

$$Cp_{ss} = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{Vc \times \alpha \times (\alpha - \beta) \times (1 - e^{-\alpha \times \tau})} +$$

$$\frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{\beta \times t_{inf}}) \times e^{-\beta \times t}}{Vc \times \beta \times (\alpha - \beta) \times (1 - e^{-\beta \times \tau})}$$

Nonsteady-State Concentration at Time t

This equation is used to predict the serum concentration (Cp) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of (K_0) over an infusion time of (t_{inf}) and a dosage interval (τ). During the infusion, t_{inf} = t.

Formulas:

$$Cp_t = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{Vc \times \alpha \times (\alpha - \beta)} +$$

$$\frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{\beta \times t_{inf}}) \times e^{-\beta \times t}}{Vc \times \beta \times (\alpha - \beta)}$$

MICHAELIS-MENTEN FORMULAS

This formula calculates the steady-state serum concentration of a drug eliminated by capacity-limited (Michaelis-Menten) pharmacokinetics (e.g., phenytoin)

$$Cp_{ss}(mg/L) = \frac{Km \times Dosage\ Rate}{(Vmax - Dosage\ Rate)}$$

where,

$$Dosage\ Rate = \frac{S \times F \times Dose}{Dosage\ Interval}$$

Dosage at Steady-State

$$Dosage = \frac{Vmax \times Cp_{ss} \times Interval}{S \times F \times (Km + Cp_{ss})}$$

Concentration at Time t

Concentrations are calculated at 1-minute intervals throughout the time range of interest for both curve fitting an graphic display. These thousands of calculations cause a slight delay in display of fitted values indicated by a horizontal progress bar.

$$\frac{Km \times Vmax}{Vmax - R} \times \ln\left(\frac{R \times Km - (Vmax - R) \times C(0)}{R \times Km - (Vmax - R) \times C(t)}\right) + C(0) - C(t) = \frac{Vmax - R}{Vd} \times t$$

where, R = S x F x Daily Dosage and C(0) is the initial plasma concentration and C(t) is the concentration at time t.

Time to Reach 90% of Steady-State Level

$$T_{90} = \frac{Km \times Vd \times (2.3 \times Vmax - 0.9 \times R)}{(Vmax - R)^2}$$

where R = S x F x Daily Dosage

CHAPTER 4. DRUG-SPECIFIC PARAMETERS

In this chapter, the formulas used to calculate the estimated pharmacokinetic parameters for individual patients are provided. In addition, certain assumptions made in the program are mentioned. Literature references are provided to document the formulas and values used.

Aminoglycosides

All of the aminoglycosides are assumed to have the same clearance and apparent volume of distribution. Parameters that are associated with aminoglycosides in the program are as follows: salt fraction = 1; bioavailability = 100 ± 5%; and the IM absorption rate constant is
1.9 hr^{-1} in patients 75 and under and 2.7 hr^{-1} in patients over 75.[1-3]

Formulas:

Clearance (L/hr):

$$CL(over\ 6\ months) = (0.82 \times CLcr + 0.11 \times dosing\ weight) \times 0.06$$

Reference: 4

$$CL(over\ 6\ months\ with\ cystic\ fibrosis) = (0.82 \times CLcr + 0.11 \times dosing\ weight) \times 0.06$$

References: 5-7

$$CL(under\ 6\ months) = (0.05 + 0.17 \times age\ in\ years) \times total\ body\ weight$$

(calculation made only if Crs is less than 0.8-1.2 mg/dL, depending on the age of the infant)

References: this equation written to smooth transition between age groups in references 5-11Volume of Distribution (L):

$$Vd(over\ 6\ months) = 0.3 \times dosing\ weight$$

$$Vd(over\ 6\ months\ to\ 1\ yr, < IBW) = 0.3 \times total\ body\ weight$$

References: 4, 12

$$Vd(1\ month\ to\ 6\ month) = (0.52 - 0.44 \times age\ in\ yr) \times total\ body\ weight$$

References: this equation written to smooth transition between age groups above and below

$$Vd(1\ month\ and\ under) = 0.52 \times total\ body\ weight$$

Reference: 13

$$Vd(1\ month\ and\ under\ receiving\ ECMO[extracorporeal\ membrane\ oxygenation]) = 0.52 \times total\ body\ weight$$

Reference: 15, 28

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 5%, CL - 50%, Vd - 30% in patients 65 and under and 50% in those over 65, CF - 50%; the time weighting factor is 1.005.[15,16] In cystic fibrosis, intrapatient variability may be increased, tending towards more normal values as infection resolves.[17-20] In these patients, the time weighting factor is increased to 1.01 in Precise PK™ to more heavily weight the most recent serum levels. Time weighting is also increased to 1.01 in critically ill and ICU patients.[21,22]

Modifying Factors

Many factors have been found to alter aminoglycoside pharmacokinetics. However, only a few have been reliably quantified and confirmed. Only those that have been well quantified are included in Precise PK™

Critically Ill or ICU Patients. Numerous studies have documented that critically ill and ICU patients have a larger volume of distribution than other patients and their variability over time is greater. Vd is increased by 13% to 0.34 L/kg in patients over 1 month of age and time weighting is increased to 1.01.[21,22]

Burn Patients. Burn patients often have higher dosage requirements than other patient groups. A major reason for this is that glomerular filtration rate is dramatically increased in some burn patients.[23] Precise PK™ allows creatinine clearance to range as high as 265 mL/min in this patient group and calculates aminoglycoside clearance as for other patients. If a burn patient is critically ill, the "Critically Ill or ICU Patient" factor should also be selected.

Hematology/Oncology Patients. These patients have an expanded Vd which is modeled as an increase of 17% to 0.35 L/kg.[24-26]

Spinal Cord Injury. These patients have a larger Vd which is increased in Precise PK™ by 10% to 0.33 L/kg.[27]

Cystic Fibrosis. Data are conflicting between studies on whether there are alterations in pharmacokinetic parameters in cystic fibrosis. One factor may be that intrapatient parameters change as therapy progresses. Precise PK™ increases the nonrenal clearance by 118%
and increases the time weighting factor to 1.01.[5-7,18,20,28]

Preterm Infants. Two factors modify the clearance if the patient is a preterm infant. Preterm infants less than 28 weeks gestational age have a clearance of 60% of full-term infants,
which increases to meet that of full-term infants at 2 months postnatal age. Preterm infants between 28 and 34 weeks gestational age have a clearance of 80% of full-term infants, which increases to meet that of full-term infants at 1 month postnatal age.

Patent Ductus Arteriosus (PDA). Newborns with uncorrected or recently treated patent ductus arteriosus have a larger volume of distribution than normal. This factor is taken into account as noted above under Volume of Distribution.[14]

ECMO. This procedure increases the volume of distribution as noted above under Volume of Distribution and decreases the clearance to 0.04 L/hr/kg.[14,28]

References

1. Chung M et al. Antimicrob Agents Chemother 1980;17:184-7.
2. Lanao JM et al. Int J Clin Pharmacol Ther Toxicol 1982;20:271-5
3. Mayer PR et al. Drug Intell Clin Pharm 1986;20:611-5.
4. Benet LZ, Sheiner LB. In Goodman AG et al., eds. The pharmacological basis of therapeutics, 7th ed. New York. Macmillan 1985:1663-733.
5. Vogelstein B et al. J Pediatr 1977;91:333-9.
6. Finkelstein E et al. J Pediatr 1979;94:163-4. Letter.
7. Levy J et al. J Pediatr 1984;105;117-24.
8. Jusko WJ et al. Kidney Int 1976;9:430-8.
9. Berry PL et al. Pediatr Pharmacol 1982;2:257-73.
10. Rohwedder H-J et al. Dtsch Med Wochenschr 1970;95:1171-4.
11. Kelman AW et al. Br J Clin Pharmacol 1984;18:685-92.
12. Tointon MM et al. Clin Pharm 1987;6:160-2.
13. Kelly HW et al. Pharmacotherapy 1990;10:238.
14. Cohen P et al. Pediatr Infect Dis J 1990;9:562-6.
15. Burton ME et al. Clin Pharmacol Ther 1985:37;349-57
16. Zaske DE et al. JAMA 1982;248:3122-6.

17. Bosso JA et al. Clin Pharm 1987;6:54-8.
18. Munzenberger PJ et al. Drug Intell Clin Pharm 1987;21:10A-1A
19. Hoppe M et al. Drug Intell Clin Pharm 1987;21:13A.
20. Horner GW et al. Drug Intell Clin Pharm 1987;21:276-8.
21. Fuhs DW et al. Clin Pharm 1988;7:207-13.
22. Dasta JF et al. Crit Care Med 1988;16:327-30.
23. Loirat P et al. N Engl J Med 1978;299:915-9.
24. Manny RP et al. Clin Pharm 1986;5:629-32.
25. Higa GM et al. Clin Pharm 1987;6:963-6.
26. Phillips JK et al. N Engl J Med 1988;319:1290.
27. Segal JL et al. Drug Intell Clin Pharm 1988;22:461-5.
28. Kearns GL et al. J Pediatr 1986;108:847-53.
29. Bhatt-Mehta V et al. Pharmacotherapy 1992;12:28-32.

Ciprofloxacin

The salt fraction for ciprofloxacin is 1 for both the oral and injectable product. Oral bioavailability is 70 ± 20% for patients 60 and younger and 87.5 ± 20% in those over 60 yr.[1-3] The absorption rate constant is 1.5.[1] Parenteral bioavailability is 100 ± 5%.

Formulas:

Clearance (L/hr):

$$CL(18\ years\ and\ over) = 1.97 \times CLcr \times 0.06 + 13.23$$

Reference: 4

Volume of Distribution (L):

$$Vd(18\ years\ and\ over) = 2.0 \times dosing\ weight$$

Reference: 6,7

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: Oral F - 20%, IV F - 5%, CL - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10% and FE is 0.25.

Modifying Factors

The absorption of oral ciprofloxacin is quite susceptible to interference by divalent cations. The amount of interference varies by product and amount contained. These products generally should be taken 6 hours before or 2 hours after ciprofloxacin.

Aluminum and Magnesium Antacids. Concurrent ingestion of these antacids reduces ciprofloxacin bioavailability by 60% per Nix DE et al. Clin Pharmacol Ther 1989;46:700-5, Shiba K et al. Antimicrob Agents Chemother 1992;36:2270-4, Flor S et al. Antimicrob Agents Chemother 1990;34:2436-8, Höffken G et al. Rev Inf Dis 1988;(suppl):S138-9.

Cancer Chemotherapy. Patients receiving cancer chemotherapy have ciprofloxacin bioavailability reduced by 47% per Johnson EJ et al. J Antimicrob Chemother 1990;25:837-42.

Cystic Fibrosis. Cystic fibrosis patients have ciprofloxacin bioavailability increased by

40%
per Cristensson BA et al. Antimicrob Agents Chemother 1992;2512-7.

Oral Didanosine. This product has buffering agents included which decrease ciprofloxacin bioavailability by 98% per Sahai J et al. Clin Pharmacol Ther 1993;53:292-7.

Oral Iron. Oral iron decreases ciprofloxacin bioavailability by 50% per Polk RE. Antimicrob Agents Chemother 1989;33:1841-4, Shiba K et al. Antimicrob Agents Chemother 1992;36:2270-4, Lehto P et al. Br J Clin Pharmacol 1994;37:82-5.

Sucralfate. Sucralfate decreases ciprofloxacin bioavailability by 60% per Garrelts JC et al. Antimicrob Agents Chemother 1990;34:931-3, Nix DE et al. Pharmacotherapy 1989;9:377-80, VanSlooten AD et al. DICP Ann Pharmacother 1991;25:578-82.

Zinc. Zinc alone or in multivitamins decreases ciprofloxacin bioavailability by 50% per Polk
RE et al. Antimicrob Agents Chemother 1989;33:1841-4.

References

1. Plaisance KI et al. Antimicrob Agents Chemother 1990;34:1031-4.
2. Ljungberg B, Nilsson-Ehle I. Eur J Microbiol Infect Dis 1989;8:515-20
3. Hirata CAI et al. Antimicrob Agents Chemother 1989;33:1927-31.
4. Drusano GL et al. Antimicrob Agents Chemother 1987;31:860-4.
5. Yuen G et al. Am J Med 1989;87(suppl 5a):70s.
6. Forrest A et al. Antimicrob Agents Chemother 1993;37:1065-72.
7. Allard S et al. Clin Pharmacol Ther 1993;54:368-73.

Digoxin

The various dosage forms of digoxin have different bioavailabilities and coefficients of variation associated with their absorption. The values used are as follows:[1,2]

	Bioavailability
Tablets	70 ± 14%
Capsules	95 ± 5%
Elixir	77.5 ± 9.6%
IV Injection	100 ± 5%

The oral absorption rate constant (ka) is set at 1.5 hr^{-1}. It should be noted that this rate constant has its primary use in determining the shape of curves plotted in the graphics portion of Precise PK™ Although Ka is used during curve fitting, serum digoxin levels should not be drawn before 6-8 hours after an oral dose when using a one-compartment simulation. Since absorption is complete by 6-8 hours after the dose, the exact value of the absorption rate constant is not important during curve fitting.

Formulas:

Clearance (L/hr):

$$CL(CHF\ over\ 10\ yr) = (0.88 \times CLcr + 0.33 \times IBW) \times 0.06$$

$$CL(nonCHF\ over\ 10\ yr) = (1.02 \times CLcr + 0.8 \times IBW) \times 0.06$$

Reference: 3

$$CL(6\ months\ to\ 10\ yr) = (1.4 \times CLcr + 0.7 \times IBW) \times 0.06$$

References: 4-8

$$CL(under\ 6\ months) = (3.2388 - 2.8777 \times age\ in\ yr) \times TBW \times 0.06$$

This equation was written to make a smooth transition between a neonatal clearance of 0.18 x total body weight and the clearance at six months.

$$CL(under\ 1\ month) = 0.18 \times TBW$$

$$CL(under\ 1\ month, premature) = 0.12 \times TBW$$

(calculation made only if Crs is less than 0.8-1.2 mg/dL, depending on the age of the infant)

Reference: all data for children under 6 months from reference 9.

Volume of Distribution (L)

$$Vd(10\ yr\ and\ over) = 3.12 \times Clcr + 3.84 \times IBW$$

Reference: 3

$$Vd(2\ yr\ to\ 10\ yr) = 16 \times IBW$$

$$Vd(1\ month\ to\ 2\ yr) = (8.44 + age\ in\ yr \times 3.78) \times total\ body\ weight$$

$$Vd(under\ 1\ month, full\ term) = 8.75 \times total\ body\ weight$$

$$Vd(under\ 1\ month, premature) = 7.5 \times total\ body\ weight$$

Reference: all pediatric data from reference 9. Equation for age group between 1 month and 2 years of age was derived to make a smooth transition between groups above and below.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - specified by product above, CL - 52%, Vd - 30%, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

A number of factors are known to affect digoxin bioavailability, clearance and apparent volume of distribution. These are used to modify the calculated population values for F, CL and Vd if they are selected as being present. The factors that are used and the references are given below:

Congestive Heart Failure. CHF decreases digoxin renal and nonrenal clearance as noted above.

Thyroid Dysfunction. Hyperthyroidism increased digoxin clearance by 30% and volume of distribution by 30%. Hypothyroidism decreases digoxin clearance by 30% and volume of distribution by 30%.[10]

Amiodarone. Amiodarone decreases digoxin clearance by an average of 28% and the volume of distribution by 12%.[11,12] It also appears to increase oral bioavailability of digoxin by an average of 25%.[13] The increased bioavailability factor is applied to the tablets and elixir only and not to the capsules.

Diltiazem. Diltiazem decreases the clearance of digoxin by 15%.[14-18]

Quinidine. Quinidine decreases the volume of distribution of digoxin by 30% and decreases the clearance by 50%.[19,20]

Verapamil. Oral verapamil decreases the nonrenal clearance by 43% during long-term use.[21,22] During the first 4 weeks of therapy, renal digoxin clearance is also decreased.[23] Therefore, total digoxin clearance will be less initially than predicted by this correction.

Amiloride or Triamterene. Amiloride and triamterene decrease nonrenal digoxin clearance by an average of 85% and increase renal clearance by 20%.[24,25]

Spironolactone. Spironolactone decreases digoxin clearance by 30%.[20,25-26]

References

1. Lanoxin product information.2. Winter ME. Basic clinical pharmacokinetics, 2nd ed., page 148.
3. Sheiner LB et al. J Pharmacokinet Biopharm 1977;5:445-79.
4. Morselli PL et al. In Morselli PL et al., eds. Basic and therapeutic aspects of perinatal pharmacology. New York. Raven Press:377-92.
5. Wettrell G et al. Acta Paediatr Scand 1974;63:705-10.
6. Gorodischer R et al. Res Commun Chem Pathol Pharmacol 1977;16:363-74.
7. Halkin H et al. Eur J Clin Pharmacol 1978;13:113-7.
8. Linday LA et al. Clin Pharmacol Ther 1981;30:735-8.
9. Wettrell G et al. Ther Drug Monit 1986;8:129-39.
10. Doherty JE et al. Ann Intern Med 1966;64:489-507.
11. Fenster JC et al. J Am Coll Cardiol 1985;5:108-12.
12. Nademanee K et al. J Am Coll Cardiol 1984;4:111-6.
13. Maragno I et al. Int J Clin Pharmacol Res 1984;4:149-53.
14 Kuhlmann J. Clin Pharmacol Ther 1985;37:150-6.
15. Jones WN et al. Eur J Clin Pharmacol 1986;31:351-3.
16. Rameis H et al. Clin Pharmacol Ther 1984;36:183-9.
17. Beltrami TR et al. J Clin Pharmacol 1985;25:390-2.
18. Yoshida A et al. Clin Pharmacol Ther 1984;35:681-5.
19. Hager WD et al. N Engl J Med 1979;300:1238.
20. Fenster PE et al. Clin Pharmacol Ther 1984;36:70-3.
21. Johnson BF et al. Clin Pharmacol Ther 1987;42:66-71.
22. Hedman A et al. Clin Pharmacol Ther 1991;49:256-62.
23. Pedersen KE et al. Eur J Clin Pharmacol 1982;22:123-7.
24. Waldorff S et al. Clin Pharmacol Ther 1981;30:172-6.
25. Waldorff S et al. Clin Pharmacol Ther 1983;33:418-23.
26. Waldorff S et al. Clin Pharmacol Ther 1978;24:162-7.

Flucytosine

The salt fraction for flucytosine is 1 for both the oral and injectable (investigational) product. Oral bioavailability is 84 ± 15% and the absorption rate constant is 1.1.[1] Parenteral bioavailability is 100 ± 5%.

Formulas:

Clearance (L/hr):

$$CL(6\ months\ and\ over) = 0.79 \times CLcr + 0.01 \times adjusted\ weight$$

References: 1-3

Volume of Distribution (L):

$$Vd(6\ months\ and\ over) = 0.71 \times adjusted\ weight$$

References: 1-4

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 15%, CL - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

There are no well-documented factors that affect flucytosine pharmacokinetics other than renal function which is accounted for in the clearance calculation above. However, it has been observed by our consultants that flucytosine serum levels of infants in intensive care units are somewhat unpredictable and are often quite low. It is not known if this is due to erratic oral absorption, instability of extemporaneously compounded flucytosine suspensions, or both. Since there are no published pharmacokinetic studies on flucytosine in infants, Precise PK™ should be used with caution in this age group.

References

1. Cutler RE et al. Clin Pharmacol Ther 1978;24:333-42.
2. Dawborn JK et al. Br Med J 1973;4:382-4.
3. Wade DN, Sudlow G. Aust N Z J Med 1972;2:153-8.
4. Schöenbeck J et al. Chemotherapy 1973;18:321-6.

Lithium

The various dosage forms of lithium salts have different bioavailabilities and absorption rate constants. The absorption rate constant has its primary relevance in determining the shape of curves plotted in the graphics portion of Precise PK™ Although it is used during curve fitting, serum lithium levels are usually drawn 12 hours after a dose. Since absorption is complete by about 10 hours after the dose, the exact value of the absorption rate constant is not important during curve fitting when using a one-compartment simulation.

Lithium Dosage Form Parameters

Dosage Form	F	SD	Ka	Refs.
Syrup	1.0	0.1	3.6	1
Fast-Release Capsules	1.0	0.1	1.2	1
Fast-Release Tablets	1.0	0.1	1.2	1
Eskalith CR	0.97	0.1	0.5	1

Formulas:

Clearance (L/hr):

$$CL(12\ yr\ or\ over) = 0.14 \times CLcr \times 0.06 + 0.006 \times adjusted\ weight$$

References: 3-8

Volume of Distribution (L)

$$Vd(12\ yr\ to\ 70\ yr) = 0.73 \times IBW$$

References: 3-5

$$Vd(over\ 70\ yr) = 0.59 \times IBW$$

References: 6,7

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - specified by product above, CL - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005. The time weighting factor is 1.005.

Modifying Factors

Acetazolamide or Sodium Bicarbonate. Acetazolamide and sodium bicarbonate increase lithium clearance by about 30% per Pepin SM, in Taylor WJ, Caviness MHD, eds. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX. Abbott Laboratories, Diagnostics Division 1986:435-65.

Angiotensin Converting-Enzyme (ACE) Inhibitors. Numerous case reports of lithium toxicity have occurred with concurrent use of these agents. However, the cause of the toxicity has not been defined and it seems to happen only sporadically. Monitor lithium serum levels especially carefully when administering an ACE inhibitor concurrently.

Ibuprofen or Piroxicam. Average clearance is decreased by 33% and the coefficient of variation is increased to 43% per Ragheb M. J Clin Psychiatr 1987;48:161-3. Ibuprofen decreases lithium clearance erratically. Data on piroxicam are limited to case reports and changes in clearance are difficult to quantify. It appears that clearance is decreased by at least 33% with piroxicam, possibly more, per Walbridge DG et al. Br J Psychiatr 1985;147:206-7 and Harrison TM et al. Br J Psychiatr 1986;149:124-5.

Diclofenac, Indomethacin or Naproxen. Diclofenac, indomethacin and naproxen decrease lithium clearance by an average of 25% per Reimann IW et al. Arch Gen Psychiatr
1983;40:283-6., Frolich JC et al. Br Med J 1979;28:1115-6 and Ragheb M et al. J Clin Psychopharmacol 1986;6:150-4.

Low Sodium Diet. A low sodium diet decreases lithium clearance by up to 50% per Atherton JC et al. Kidney Int 1990;37(suppl 28):S36-8.

Theophylline. The clearance of lithium is increased proportionately to theophylline serum concentration. An increase in lithium clearance of 50% corresponds approximately to a theophylline level of 15 mg/L per Holstad SG et al. Psychiatry Res 1988;25:203-11.

Thiazide Diuretics. Thiazides in typically used doses decrease lithium clearance by an average of 29% per Petersen V et al. Br Med J 1974;2;143-5., Himmelhoch JM et al. Clin Pharmacol Ther 1977;22:225-7 and Jefferson JW et al. JAMA 1979;241:1134-6.

References

1. Amdisen A, Carson SW. In, Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principles of therapeutic drug monitoring, 2nd Ed. Spokane. Applied Therapeutics. 1986:978-1008.
2. Vitiello B et al. J Clin Psychopharmacol 1988;8:355-9.
3. Groth U et al. Clin Pharmacol Ther 1974;16:490-8.
4. Mason RW et al. Clin Pharmacokinet 1978;3:241-6.
5. Hunter R. Br J Clin Pharmacol 1988;25:375-80.

6. Chapron DJ et al. J Am Geriatr Soc 1982;30:651-5.
7. Hardy BG et al. J Clin Psychopharmacol 1987;7:153-8.
8. Clericetti N et al. Clin Nephrol 1991;36:281-9.

Levofloxacin and Ofloxacin

The salt fraction for ofloxacin is 1 for both the oral and injectable product. Oral bioavailability is 100 ± 10%. The absorption rate constant is 3.0.[1,2] Parenteral bioavailability is 100 ± 5%.

Formulas:

Clearance (L/hr):

$$CL(18\ yr\ or\ over) = (1.21 \times CLcr + 36) \times 0.06$$

References: 3

Volume of Distribution (L)

$$Vd(18\ yr\ or\ over) = 1.36 \times dosing\ weight$$

References: 4-8

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: Oral F - 10%, IV F -
5%, CL - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10%
and FE is 0.15.

Modifying Factors

The absorption of oral levofloxacin and ofloxacin is susceptible to interference by divalent cations. The amount of interference varies by product and amount contained. These products generally should be taken 6 hours before or2hours after lovofloxacin or ofloxacin.

Aluminum and Magnesium Antacids. Concurrent ingestion of these antacids reduces ofloxacin bioavailability by 45% per Flor S et al. Antimicrob Agents Chemother 1990;34:2436-8, Höffken G et al. Rev Infect Dis 1998:(suppl):S138-9 (abstract) and decreases the Ka to 0.67/hr per Akerele JO, Okhamafe AO. J Antimicrob Chemother 1991;28:87-94.

Oral Iron. Oral iron decreases ofloxacin bioavailability by 17.5% and increases the SD to
15% per Lehto P et al. Br J Clin Pharmacol 1994;37:82-5, Martinez Cabarga M et al. Antimicrob Agents Chemother 1991;35:2102-5.

Sucralfate. Sucralfate decreases ofloxacin bioavailability by 61% per Lehto P et al. Antimicrob Agents Chemother 1994;38:248-51.

References

1. Yuk JH et al. Antimicrob Agents Chemother 1991;35:384-6.
2. Sanchez Navarro A et al. Antimicrob Agents Chemother 1990;34:455-9.
3. Lameire N et al. Clin Pharmacokinet 1991;21:357-71.
4. Höffler D, Koeppe P. Drugs 1987;34(suppl 1):51-5.
5. Farinotti R et al. Antimicrob Agents Chemother 1998;32:1590-2.
6. Lode H et al. Antimicrob Agents Chemother 1987;31:1338-42.
7. Yuk JH et al. Antimicrob Agents Chemother 1991;35:384-6.
8. Sanchez Navarro A et al. Antimicrob Agents Chemother 1990;34:455-9.

Phenobarbital

The salt fraction is 1 for the oral product and 0.91 for the injectable product. Oral bioavailability is 100 ± 10%, while parenteral bioavailability is 100 ± 5%. Absorption rate constants are 1.5 hr^{-1} for tablets, 7.2 hr^{-1} for the elixir and 1.1 hr^{-1} for IM injections.[1,2]

Formulas:

Clearance (L/hr):

$$CL(over\ 13\ yr) = 0.004 \times total\ body\ weight$$

References: 3-6

$$CL(10\ to\ 13\ yr) = (0.0077 - (age\ in\ yr - 10) \times 0.0012333) \times total\ body\ weight$$

Reference: this equation was written to make a smooth transition between age groups above and below as suggested by data in reference 7.

$$CL(1\ month\ to\ 10\ yr) = 0.0077 \times total\ body\ weight$$

References: 6-10

$$CL(1\ month\ and\ under) = (0.005 + 0.0325 \times age\ in\ yr) \times total\ body\ weight$$

References: This equation was written to make a smooth transition between values for newborns and 1 month-old infants as suggested by data in references 17 and 18.

Volume of Distribution (L)

$$Vd(over\ 1\ month) = 0.6 \times total\ body\ weight$$

References: 10-13

$$Vd(1\ month\ and\ under) = (0.91 - 3.7 \times age\ in\ yr) \times total\ body\ weight$$

Reference: this equation was written to make a smooth transition between Vd of 0.6 L/kg above and neonatal Vd of 0.91 L/kg per references 10-13.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 10%, CL - 20% in adults and 40% in children under 13 and in those taking valproate,[3,6,14] Vd - 10% in adults and 20% in children under 13, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

Liver Disease. Severe cirrhosis decreases phenobarbital clearance by one-third while hepatitis decreases clearance by 17%.[15]

Pregnancy. Pregnancy increases clearance by an estimated 35% from data of reference 16.

Valproic Acid. Concurrent valproic acid use decreases phenobarbital clearance by 35% in adults and 55% in children under 16.[3,6,14]

References

1. Wilensky AJ et al. Eur J Clin Pharmacol 1982;23:87-92.
2. Meyer MC et al. J Pharm Sci 1984;73:485-8.
3. Patel IH et al. Clin Pharmacol Ther 1980;27:515-21.
4. Nelson E. et al. J Clin Pharmacol 1982;22:141-8.
5. Wilensky AJ et al. Eur J Clin Pharmacol 1982;23:87-92.
6. Fernandez de Gatta MR et al. Ther Drug Monit 1986;8:416-20.
7. Beck DE et al. Clin Pharm 1986;5:754-9.
8. Davis AG et al. Pediatrics 1981;68:824-7.
9. Jalling B. Develop Med Child Neurol 1974;16:781-93.
10. Pitlick W et al. Clin Pharmacol Ther 1978;23:346-50.
11. Fischer JH et al. Neurology 1981;31:1042-4.
12. Painter MJ et al. J Pediatr 1978;92:315-9.
13. Boreus LO et al. in Morselli PL et al eds. Basic and therapeutic aspects of perinatology. New York. Raven Press. 1975.
14. Suganuma T et al. J Pediatr 1981;99:314-7.
15. Alvin J et al. J Pharmacol Exp Ther 1975;192:224-35.
16. Dam M et al. Clin Pharmacokinet 1979;4:53-62.
17. Pitlick W et al. Clin Pharmacol Ther 1978;23:346-50.
18. Alonso Gonzalez AC et al. J Clin Pharm Ther 1993;18:267-70.

Phenytoin

Phenytoin exhibits slow and erratic (although usually complete) oral absorption, variable plasma protein binding, and capacity-limited (Michaelis-Menten) elimination pharmacokinetics. All of these factors contribute to the great difficulty in predicting an individual patient's phenytoin dosage requirements. Various condition and drugs are known to affect phenytoin's pharmacokinetics, although the exact changes in parameters is often not known. Because of these many factors and their uncertainty, Precise PK™ groups some of these factors together and makes a single approximate change in pharmacokinetic parameters. It is always important to measure serum phenytoin levels during therapy, especially if there are complicating factors. Obtaining free (unbound) phenytoin levels are particularly recommended in the presence of drugs or conditions that affect protein binding. Phenytoin injection should not be given intramuscularly because of its poor absorption and tissue toxicity. Only the phenytoin prodrug fosphenytoin is allowed to be given IM by Precise PK™ It is converted to phenytoin in the body by a first-order process.

Absorption

Oral phenytoin absorption in adults is modeled as a constant 60 mg/hour. The concept of this absorption model was introduced by McCauley et al.[8] The value of 60 mg/hour is an average derived from references 9-12 and data from patients at UC San Diego Medical Center. In children under 18 years, the absorption rate is modeled as 1 mg/kg/hour. Intramuscular fosphenytoin absorption (ref. 1) has a Ka of 2.5 and intravenous fosphenytoin absorption has a Ka of 3.6 (ref. 2) which represents conversion to phenytoin. The History Spreadsheet Screen (Chapter 1, Figure 10) allows two oral dosage forms to be entered. The regimen of
each dosage form must be specified on separate lines using the letters Capsule, Suspension or
Tablet in the Route box of the spreadsheet to designate the corresponding dosage form.

Phenytoin Dosage Form Parameters

Dosage Form	S	F	SD	Refs
Fosphenytoin (IM)	0.92*	1	0.1	1
Fosphenytoin (IV)	0.92*	1	0.1	2
Phenytoin Injection (IV)	0.92	1	0.1	3
Phenytoin Capsules	0.92	1	0.1	3
Phenytoin Suspension	1	1	0.1	3
(neonates <1 month)	1	0.9	0.2	4
Phenytoin Tablets	1	1	0.1	3

*Dosage expressed in phenytoin sodium equivalents (PE)

Phenytoin Plasma Protein Binding

Group	Unbound Fraction (α)*	Refs.
Adults and Children		
CLcr > 25 mL/min	1 / (1 + albumin x 2.05)	3
CLcr 10-25 mL/min	1 / (1 + albumin x (1 + [0.07 x {CLcr - 10}]))**	
CLcr <10 mL/min	1 / (1 + albumin)	3
Neonates <1 month	0.2	5

* to fit unbound phenytoin levels, enter 0.01 as the serum albumin concentration on the Patient Demographics screen

**equation to smooth transition between normal and uremic values

Population Estimates:

Vmax (mg/day):

$$Vmax(< 6\ yr) = \frac{11.5mg}{day} \times total\ body\ weight$$

References: 3,4

$$Vmax(6\ yr\ to\ 18\ yr) =$$
$$[805 - 25 \times (\text{patient age} - 6)] \times (\frac{total\ body\ weight}{70kg})^{0.6}$$

Reference: Ref. 3 with equation written to smooth transition between upper and lower age groups and weight adjustment per ref. 13

$$Vmax(>\ 18\ yr) =$$
$$[500 - 1.5 \times (\text{patient age} - 18)] \times (\frac{total\ body\ weight}{70kg})^{0.6}$$

Reference: Ref. 3 with equation written to smooth transition between upper and lower age groups and weight adjustment per ref. 13

Km (mg/L):

$$Km(< 1\ month) = 5\text{mg/L}$$

Reference:4

$$Km(1\ month\ to\ 6\ months) = 5 + 0.3 \times (\text{age in yr} - 0.083)$$

Reference: Equation written to smooth transition between upper and lower age groups.

$$Km(6\ months\ to\ 15\ yr) = 6.4\text{mg/L}$$

Reference: 14 (weighted average of all groups)

$$Km(> 15\ yr) = 5.7\text{mg/L}$$

Reference: 13

Volume of Distribution (L)

$$Vd(\leq 1\ yr) = 1 \times TBW \pm 30\%$$

Reference: 3

$$Vd(> 1\ yr) \quad if\ (TBW \leq IBW)\ Vd = 0.65 \times TBW$$
$$if\ (TBW > IBW)\ Vd = 0.65 \times [IBW + 1.33 \times (TBW - IBW)]$$

Reference: 3,15

Correction of Serum Levels and Vd to Normal Albumin Concentration and Affinity

For CLcr < 25 mL/min:

$$Corrected\ Parameter = \frac{Uncorrected\ Parameter}{0.48 \times (1-\alpha) \times serum\ albumin/4.4 + \alpha}$$

For CLcr >= 25

$$Corrected\ Parameter = \frac{Uncorrected\ Parameter}{(1-\alpha) \times serum\ albumin/4.4 + \alpha}$$

Correction of Serum Level Range and Km for Altered Albumin Concentration and Affinity

For CLcr < 25 mL/min:

$$Corrected\ Parameter = Uncorrected\ Parameter \times 0.48 \times (1-\alpha) \times serum\ albumin/4.4 + \alpha$$

For CLcr >= 25 mL/min:

$$Corrected\ Parameter = Uncorrected\ Parameter \times [(1-\alpha) \times serum\ albumin/4.4 + \alpha]$$

Curve Fitting

Curve fitting of phenytoin varies somewhat for phenytoin compared to other drugs in

Precise PK™. Because there is no direct mathematical method for calculating the concentration at any given time after a dose, a unique iterative method is used (see Michaelis-Menten Formulas in Chapter 3. Pharmacokinetic Formulas). Also, because more parameters are fitted and the number of serum levels may be few, and because most published reports in the literature use Bayesian methods, Precise PK™ uses only Bayesian curve fitting; least-squares is not available. In addition, levels are not time-weighted in order to preserve as much serum level data as possible.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 10%, Vmax - 30%, Km - 50%, Vd - 20%, CF - 50%. The assay error is 10% and FE is 0.75.

Modifying Factors

Ethnic Differences. Metabolism of phenytoin is under genetic control. Various ethnic groups appear to metabolize phenytoin differently. However, it is unclear the extent to which genetic and environmental (e.g., diet, pollution) factors contribute to these differences, which groups are affected and by how much. The best studied group is Japanese patients (in Japan) who have a lower Km than Europeans; Japanese-Americans have not been studied. Some evidence also exists that Blacks in southern Africa have similarly prolonged elimination. African-Americans appear to have metabolism more similar to Caucasians than to southern Africans. Saudi Arabians' metabolism seems to be similar to Caucasians'. Hvidberg EF. Ethnic differences in reactions to drugs and xenobiotics. Alan R. Liss, Inc. 1986:279-87; Edeki TI, Brase DA. Drug Metab Rev 1995;27:449-69; Botha JH et al. Clin Pharm
1991;10:928-31; Grasela TH et al. Clin Pharmacokinet 1983;8:355-64. Precise PK™ allows selection of a slow metabolism factor for patients who have ethnically slow metabolism; Km is decreased by 50% if this option is selected.

Highly Protein-Bound Drugs. Drugs that are highly albumin bound can increase the free (unbound) fraction of phenytoin. The free fraction is increased by 50% in Precise PK™ with valproic acid concentration over 70 mg/L. The value arises from the 50% change that occurs with moderate serum levels of valproic acid per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 2005:267-85

Jaundice. The free fraction is increased by 50% with a serum bilirubin >6 mg/dL. This value is estimated from the fact that a serum bilirubin of 6 mg/dL is over 0.1 mmol/L, per Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 2nd ed. Applied Therapeutics. Vancouver, WA. 1986.

Neurologic Injury. Critically ill patients with head trauma have high phenytoin requirements. This appears to be caused primarily by an increase in predicted Vmax by 40%. Boucher BA et al. Clin Pharmacol Ther 1988;44:675-83 and O'Mara NB et al. Crit Care
Med 1995;23:1418-24.

Tube Feeding. Tube feeding has marked effects on phenytoin levels. In Precise PK™, it is modeled as a decrease in F to 0.6 and an increase in its SD to 0.3 per the computer program, Phenda. Boucher BA et al. Clin Pharm 1987;6:881-7.

Other Factors

Many other factors are known to affect phenytoin serum concentrations. However, the exact effects on pharmacokinetic parameters are not known. They probably also increase the variability in the factors they affect. The following factors are not programmed into Precise PK™, but the user may consider manually adjusting these parameters and/or increasing their SD in patients with one of these conditions.

Antacids or Sucralfate. Antacids or sucralfate may decrease bioavailability (F) of phenytoin. It is best to separate doses of phenytoin and antacids by 2 or more hours per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

Cirrhosis or Severe Liver Disease. Liver diseases may reduce phenytoin's metabolism, causing a decrease in Vmax per Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 4th ed. Lippincott Williams & Wilkins. Baltimore. 2006.

Diarrhea. Diarrhea may decrease the absorption (F) of phenytoin per Winter M. in Murphy
J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

Fluoxetine, Fluconazole and Voriconazole. These drugs have been relatively well document to increase phenytoin AUC by about 75% per Drug Interactions Facts. Wolters Kluwer Health, Inc. 2008. This change is modeled as an increase in Km by 75% in Precise PK.

Other Enzyme Inhibiting Drugs. Drugs that competitively inhibit hepatic cytochrome P450 metabolism of phenytoin, increasing its Km. These drugs do not have adequate documentation to allow specific changes to phenytoin parameters in Precise PK. Common drugs included in this category include: amiodarone, fluvastatin (possibly), chloramphenicol, cimetidine, clarithromycin (possibly), disulfiram, isoniazid (especially in slow acetylators), omeprazole, sulfonamides, ritonavir, trimethoprim, valproic acid (possibly), and zafirlukast (possibly) per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209 & Anderson PO. Cytochrome P450 enzyme interactions. In, Anderson PO, Knoben JE, eds. Handbook of clinical drug data, 8th ed. Stamford, CT. Appleton & Lange; 1997:694-6.

Enzyme-Inducing Drugs. Drugs that induce hepatic cytochrome P450 metabolism of phenytoin increase Vmax and/or decrease Km. These drugs do not have adequate documentation to allow specific changes to phenytoin parameters in Precise PK. Common drugs included in this category include: carbamazepine, phenobarbital (usually an inducer, but sometimes a competitive inhibitor), and rifampin. Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209 & Anderson PO.

Cytochrome P450 enzyme interactions. In, Anderson PO, Knoben JE, eds. Handbook of clinical drug data, 8th ed. Stamford, CT. Appleton & Lange; 1997:694-6.

References

1. Boucher BA et al. J Pharm Sci 1989;78:929-32.
2. Fierro LS et al. Am J Health-Syst Pharm 1996;53:2702-12.
3. Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 4th ed. Lippincott Williams & Wilkins. Baltimore. 2006
4. Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.
5. Painter MJ et al. J Clin Pharmacol 1994;34:312-7.
6. Winter M. Basic clinical pharmacokinetics, 2nd ed, Vancouver, WA. Applied Therapeutics. 1988:237.
7. Vanholder R et al. Kidney Int 1988;33:996-1004.
8. McCauley DL et al. Ther Drug Monit 1989;11:540-2.
9. Ratanakorn D et al. J Neurol Sci. 1997;147:89-92.
10. Randinitis EJ et al. Epilepsia. 1990;31:458-64.
11. Smith TC, Kinkel A. Clin Pharmacol Ther. 1976;20:738-42.
12. Jung D et al. Clin Pharmacol Ther. 1980;28:479-85.
13. Grasela TH et al. Clin Pharmacokinet 1983;8:355-64
14. Bauer LA, Bluin RA. Clin Pharmacokinet 1983;8:545-9.
15. Abernethy DR, Greenblatt DJ. Arch Neurol 1985;42:468-71.

Procainamide

Procainamide Dosage Form Parameters

Dosage Form	F	SD	Ka	Refs.
Fast-Release Capsules	0.83	0.166	2	1,2
Slow-Release Capsules	0.83	0.166	0.4	1,3,4

Formulas:

Clearance (L/hr):

$$CL(over\ 12\ yr) = (2.7 \times CLcr + 3.9 \times adjusted\ weight) \times 0.06$$

References: 2

$$CL(7\ to\ 12\ yr) = 1.94 \times total\ body\ weight$$

Reference: 5

$$CL(6\ months\ to\ 7\ yr) = 7.3 + 1.86 \times (age\ in\ yr - 0.5) \times total\ body\ weight$$

Reference: this equation was written to make a smooth transition between age groups above and below.

$$CL(under\ 6\ months) = 7.3 \times total\ body\ weight$$

Reference: 6

Volume of Distribution (L)

$$Vd(18\ yr\ and\ above) = 1.9 \times adjusted\ weight$$

References: 2

$$Vd(12\ to\ 18\ yr) = [2.9 - (age\ in\ yr - 12) \times 0.166] \times adjusted\ weight$$

References: this equation was written to make a smooth transition between age groups above and below.

$$Vd(12\ yr\ and\ under) = 2.9 \times total\ body\ weight$$

References: 5,6

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 20%, CL - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10% and FE is 0.35.

Modifying Factors

Amiodarone. Amiodarone decreases total drug clearance by 23% per Windle J et al. Clin Pharmacol Ther 1987;41:603-10 and Saal AK et al. Am J Cardiol 1984;53:1264-7.

Cimetidine. Cimetidine decreases renal clearance by 40% per nonrenal clearance per Bauer LA et al. JAGS 1990;38:467-9, Somogyi A et al. Eur J Clin Pharmacol 1983;25:339-45, Rodvold KA. Ther Drug Monit 1987;9:378-83, Lai, MY et al. Int J Clin Pharmacol Ther Toxicol 1988;26:118-21 and Christian CD et al. Clin Pharmacol Ther 1984;36:221-7.

Trimethoprim or Septra. Trimethoprim decreases procainamide renal clearance by 46% per Vlasses PH et al. Arch Intern Med 1989;149:1350-3, Kosoglou T et al. Clin Pharmacol Ther 1988;44:467-77.

Impaired Cardiac Output. Decreased cardiac output decreases total drug clearance by 35% per Winter M. Basic clinical pharmacokinetics, 2nd ed, Vancouver, WA. Applied Therapeutics. 1988.

References

1. Coyle JD, Lima JJ. In, Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics: principles of therapeutic drug monitoring, 2nd Ed. Spokane; 199--:22-3 to 22-33.
2. Benet LZ, Sheiner LB. In Goodman AG et al, eds. The pharmacological basis of therapeutics, 8th ed. New York. Macmillan 1990:1703.
3. Tilstone WJ et al. Eur J Clin Pharmacol 1978;14:261-5.
4. Baker BA et al. Clin Pharm 1988;7:135-8.
5. Singh S et al. Clin Pharmacol Ther 1982;32:607-11.
6. Bryson SM et al. DICP Ann Pharmacother 1991;25:68-71.

Quinidine

Quinidine has a number of factors associated with its bioavailability. There are several salt forms each containing different amounts of quinidine base. Each dosage form also has an associated absorption rate constant and bioavailability. Certain factors can also affect these absorption parameters.

Oral Quinidine Parameters

Dosage Form	Salt	F	Ka	Refs.
Quinidine Sulfate (nonsustained-release tablets and capsules)	0.83	0.8[+]	1.8[*]	1-4
Cardioquin	0.6	0.8[+]	1.15[*]	1
Quinaglute	0.625	0.8[+]	0.7[*]	1,5-7
Duraquin	0.625	0.8[+]	0.5[*]	4,8,9
Quinidex	0.83	0.8[+]	0.34[*]	1,10-13

Intramuscular Quinidine Parameters

Quinidine Gluconate	0.625	0.875	0.77[*]	3
Quinidine Sulfate		0.83	0.875	0.77[*] 3

[+]Concurrent rifampin use increases the first-pass metabolism of quinidine and decreases oral bioavailability by 41%.[14]
[*]Congestive heart failure decreases the rate of absorption of oral quinidine by 45%;[15] IM quinidine absorption is slowed by 56%.[16]

Formulas:

Clearance (L/hr):

$$CL(over\ 60\ yr\ and > 50kg) = 0.0566 \times CLcr + 10$$

References: 5,17

$$CL(12\ to\ 60\ yr\ or\ elderly\ adults < 50kg) = 0.0566 \times CLcr + 0.2 \times adjusted\ weight$$

Reference: 17-20

$$CL(9\ to\ 12\ yr) = [0.46 - (age\ in\ yr - 9) \times 0.57] \times adjusted\ weight$$

References: this equation was written to smooth the transition between values for

children age 9 years and under to those of 12 year olds which appear to be equal to weight-adjusted adult values based on data in reference 19.

$$CL(6\ months\ to\ 9\ yr) = 0.46 \times adjusted\ weight$$

Reference: 19

Volume of Distribution (L):

$$CL(over\ 6\ months) = 2.7 \times adjusted\ weight$$

Reference: 4

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 15%, CL - 45%, Vd -
40%, CF - 50%. The time weighting factor is 1.005.

Serum Level Range

The therapeutic serum level range of quinidine is not firmly established and depends to a certain extent on the assay method used. The range used in Precise PK™ (1-4 mg/L) is for *unchanged* quinidine and is most relevant for newer, more specific assay techniques such as HPLC. Older, less specific assays, such as the fluorescent assay, also detect certain metabolites, some of which may have partial activity. The therapeutic range with these latter assays is accordingly higher (2-6 mg/L). The assay method and usual therapeutic range of users laboratory should be taken into account when using Precise PK™

Modifying Factors

Congestive Heart Failure. CHF decreases the volume of distribution by 32% and decreases nonrenal clearance by 46% or total clearance by an average of 34%.[17,21] Absorption rates are also affected as noted above.

Cirrhosis. Cirrhosis increases the volume of distribution by 50%.[22] Severe cirrhosis may also decrease nonrenal clearance (by 46%),[17] but this factor is not included in Precise PK™ because is was derived in only three patients and older studies found no such decrement.[22]

Amiodarone. Amiodarone increases quinidine serum levels by perhaps as much as 100%.[23] The exact mechanism of this interaction is currently unknown. Precise PK™ currently assumes that this is due to a 50% decrease in clearance.

Barbiturates. Barbiturates increase clearance of quinidine by 2.5 times and increase the variability of clearance by 20%.[24]

Cimetidine. Cimetidine decreases quinidine clearance by 40%.[25]

Phenytoin. Phenytoin increases clearance of quinidine by 2.5 times and increases the variability of clearance by 20%.[24]

Rifampin. Rifampin increases clearance by 3.7 times.[14] It also decreases oral bioavailability as noted above.

Verapamil. Preliminary evidence indicates that verapamil decreases quinidine clearance by 35%.[26,27]

References

1. Unpublished data by Riegelman S et al. from a report submitted to the FDA September 1977. Obtained in a personal communication from Robert Upton, Ph.D., University of California School of Pharmacy, April 23, 1986.
2. Personal communication, Mary Jo Brandt, M.D., Lilly Research Laboratories, February 13, 1986.
3. Ochs HR et al. Clin Pharmacokinet 1980;5:150-68.
4. Benet LZ, Sheiner LB. In Goodman AG et al. eds. The pharmacological basis of therapeutics, 7th ed. New York. Macmillan 1985:1663-733.
5. Ochs HR et al. Am J Cardiol 1978;41:770-7.
6. Spenard J et al. Int J Clin Pharmacol Ther Toxicol 1983;21:1-9.
7. Sirois G et al. Biopharm Drug Disp 1980;1:167-77.
8. Estimates from graphic data supplied by Parke-Davis.
9. Smith TC et al. Curr Ther Res 1977;21:128-34.
10. Wright GJ. Unpublished bioavailability study. A.H. Robins.
11. Gibson DL et al. Clin Pharm 1982;1:366-8.
12. Sawyer WT et al. Biopharm Drug Disp 1982;3:301-10.
13. Mahon WA et al. Clin Pharmacokinet 1987;13:118-24.
14. Twum-Barima Y et al. N Engl J Med 1981;304:1466-9.
15. Ueda CT et al. Br J Clin Pharmacol 1981;11:571-7.
16. Couthamel WG. Am Heart J 1975;90:335-9.
17. Fattinger K et al. Br J Clin Pharmacol 1991;31:279-86.
18. Ochs HR et al. Am J Cardiol 1978;42:481-5.
19. Szefler SJ et al. Pediatrics 1982;70:370-5.
20. Guentert TW et al. J Pharmacokinet Biopharm 1979;7:315-30.
21. Ueda CT et al. Clin Pharmacol Ther 1978;23:158-64.
22. Kessler KM et al. Am Heart J 1978;96:627-35.
23. Saal AK et al. Am J Cardiol 1984;53:1264-7.
24. Hansten PD. Drug Interactions, 5th Ed. New York Macmillan. 1985.
25. Hardy BG et al. Am J Cardiol 1983;52:172-5.
26. Edwards DJ et al. Clin Pharmacol Ther 1987;41:68-73.
27. Trohman RG et al. Am J Cardiol 1986;57:706-7.

Theophylline

Absorption parameters for the theophylline derivatives include the salt form (salt), the bioavailability (F) and its coefficient of variation (CV), the absorption rate constant (Ka), and the time to 90% absorption (t_{90}). The values for specific products are listed in the table on the following page. In Precise PK™, all oral dosage forms are modeled as if absorption were a first-order process (i.e., using Ka). While some of the better slow-release dosage forms approach true zero-order absorption, with the slow absorption rate constants used, differences in predictions between the two models are clinically unimportant.

Absorption rate constants were primarily calculated from data that were visually obtained from Wagner-Nelson absorption plots. Both the time to 50% absorption (1 half-life) and the time to 90% absorption (3.5 half-lives) were read off the plots and the derived constants were averaged to produce the Ka. In a few instances, investigators reported the time to 50% absorption and this value was used to calculate Ka. Whenever possible, several studies and methods were used to derive Ka. Average values of the best data are used for Ka in Precise PK™. The theophylline pharmacokinetic parameters used in Precise PK™ are presented with references in tabular form below.

Formulas:

Clearance (L/hr):

$$CL(over\ 60\ yr) = 0.035 \times total\ body\ weight$$

Reference: 12

$$CL(18\ to\ 60\ yr) = 0.04 \times total\ body\ weight$$

Reference: 12-17

$$CL(18\ to\ 60\ yr, obese) = 0.032 \times total\ body\ weight$$

Reference: 14-16

$$CL(10\ to\ 18\ yr) = [0.084 - 0.0055 \times (age\ in\ yr - 10)] \times adjusted\ weight$$

Reference: this equation was written to make a smooth transition between age groups above and below as suggested by data in reference 12.

$$CL(1\ to\ 10\ yr) = 0.084 \times adjusted\ weight$$

Reference: 12,18

$$CL(under\ 1\ yr) = (0.018 + 0.066 \times age\ in\ yr) \times adjusted\ weight$$

Reference: this equation was written to make a smooth transition between the clearance of the age group above and the clearance of 0.018 x total body weight at birth, per references 19 and 20.

Theophylline Dosage Form Parameters

Dosage Form	Salt	F	SD	Ka	t_{90}	Ref.
Elixir/Syrup	1	1	0.1	2.3	-	1,2
Fast-Release Solids	1	1	0.1	2.4	-	1,2
*Theo-24 (fasting)	1	0.65	?	0.03-0.8	30^{+}	3,9
*Theo-24 (meal)	1	1	?	0.125	20	9
Aminophylline Parameters						
Injection	0.79	1	-	-	-	10
Elixir/Syrup	0.86	1	0.1	2.3	-	1,2,11
Fast-Release Tablets	0.8	0.94	0.1	2.4	-	1,2,11

*These products are erratically absorbed, with large differences between the fasting and nonfasting states.[8-10] They are not included as menu selections in Precise PK™ for this reason.

Volume of Distribution (L):

$$Vd(under\ 1\ month) = 0.77 \times total\ body\ weight$$

Reference: 19

$$Vd(1\ month\ to\ 1\ yr) = (0.8 - 0.31 \times age\ in\ yr) \times total\ body\ weight$$

Reference: this equation was written to make a smooth transition between age groups above and below.

$$Vd(1\ yr\ and\ over, nonobese) = 0.48 \times total\ body\ weight$$

Reference: 13-17

$$Vd(1\ yr\ and\ over, obese) = 0.35 \times total\ body\ weight$$

Reference: 13-17

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are follows: F - specified by product above, CL - 50%, Vd - 25% , CF - 50%. The time weighting factor is 1.01.[21]

Modifying Factors

Congestive Heart Failure. Congestive heart failure decreases theophylline clearance to 43% of normal.[22]

Cirrhosis. Cirrhosis decreases theophylline clearance by 50%[23]

Chronic Obstructive Pulmonary Disease. COPD decreases theophylline clearance to 80% of normal.[22]

Smoking. Smoking increases theophylline clearance to 1.6 times normal.[22]

Cimetidine. Cimetidine use decreases theophylline clearance to 75% of normal.[24,25]

Ciprofloxacin or Erythromycin. Concurrent ciprofloxacin use decreases theophylline clearance by 25%.[26-28] Concurrent erythromycin use also decreases theophylline clearance by about 25% after 5 days of use.[29-31]

Oral Contraceptives. Oral contraceptives decrease theophylline clearance by 30%.[32]

Phenytoin. Concurrent phenytoin use increases theophylline clearance to 1.5 times normal.[33]

Rifampin. Rifampin increases theophylline clearance by 45%.[34-37]

Mexiletine or Troleandomycin. Concurrent mexiletine or troleandomycin use decreases theophylline clearance by about 50%.[38,39]

Cystic Fibrosis. Cystic fibrosis increases theophylline clearance by 1.8 times and increases volume of distribution by 30%.[40,41]

Phenobarbital. Chronic phenobarbital use increases theophylline clearance by 33%.[24]

Diltiazem or Verapamil. Diltiazem and verapamil each decrease theophylline clearance by about 15%.[42-44]

Thyroid Dysfunction. Theophylline clearance is increased by 40% in hyperthyroidism, while hypothyroidism decreases clearance by 20% and increases volume of distribution by 40%.[45,46]

References

1. Fagerstrom PO et al. Int J Clin Pharmacol Ther Toxicol 1983;21:359-62.
2. Jonkman JHG et al. Eur J Clin Pharmacol 1980;17:379-84.
3. Hendeles L et al. Clin Pharmacokinet 1984;9:95-135.

4. Upton RA et al. J Pharmacokinet Biopharm 1980;8:131-49.
5. Williams RL et al. Curr Ther Res 1982;31:45-55.
6. Williams RL et al. J Asthma 1983;20:27-30.
7. Saccar Cl et al. Ann Allergy 1983;50:245-8.
8. Pedersen S et al. Pediatrics 1984;74:534-8.
9. Hendeles L et al. Chest 1985;87:758-65.
10. Karim A et al. Clin Pharmacol Ther 1985;38:642-7.
11. American Hospital Formulary Service. Drug Information 85:1675-7.
12. Hendeles L et al. Pharmacotherapy 1983;3:2-44.
13. Benet LZ, Sheiner LB. In Goodman AG et al. eds. The pharmacological basis of therapeutics, 7th ed. New York. Macmillan 1985:1663-733.
14. Gal P et al. Clin Pharmacol Ther 1978;23:438-44.
15. Blouin RA et al. Clin Pharmacol Ther 1980;28:619-23.
16. Rohrbaugh TM et al. Pediatr Pharmacol 1982;2:75-83.
17. Jewesson PJ et al. Ther Drug Monit 1985;7:197-201.
18. Kubo M et al. J Pediatr 1986;108:1011-5.
19. Gilman JT et al. Ther Drug Monit 1986;8:4-10.
20. Nassif EG et al. J Pediatr 1981;98:158-61.
21. Peck CC et al. Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care, 988-94.
22. Powell JR et al. Am Rev Resp Dis 1978;118:229.
23. Piafsky KM et al. N Engl J Med 1977;296:1495-7.
24. Jonkman JHG et al. Clin Pharmacokinet 1984;9:309-34.
25. Cohen IA et al. Ther Drug Monit 1985;7:426-34.
26. Schwartz J et al. Antimicrob Agents Chemother 1988;32:75-7.
27. Wijnands WJA et al. Pharm Weekbl [Sci] 1987;9(suppl):72-5.
28. Nix DE et al. J Antimicrob Chemother 1987;19:263-9.
29. Cummins DP et al. Ann Allergy 1976;37:450-1.
30. Kozak P et al. Clin Immunol 1977;16:149-51.
31. Prince RA et al. J Clin Pharmacol 1989;29:650.
32. Baciewicz AM. Ther Drug Monit 1985;7:26-35.
33. Ogilvie RI. Clin Pharmacokinet 1978;3:267-93.
34. Robson RA et al. Br J Clin Pharmacol 1984;18:445-8.
35. Straughn AB et al. Ther Drug Monit 1984;6:153-6
36. Powell-Jackson PR et al. Am Rev Resp Dis 1985;131:939-40.
37. Boyce EG et al. J Clin Pharmacol 1986;26:696-9.
38. Weinberger M. J Allergy Clin Immunol 1977;59:228-31.
39. Loi C-H et al. Clin Pharmacol Ther 1991;49:571-80.
39. Isles A et al. Am Rev Resp Dis 1981;127;417-21.
40. Knoppert DC et al. Clin Pharmacol Ther 1988;44:254-64.
41. Nafziger AN et al. J Clin Pharmacol 1987;27:862-5.
42. Robson RA et al. Br J Clin Pharmacol 1988;25:397-400.
43. Sirmans SM et al. Clin Pharmacol Ther 1988;44:29-34.
44. Vozeh S et al. Clin Pharmacol Ther 1984;36:634-40.
45. Pokrajak M et al. Eur J Clin Pharmacol 1987;33:483-6.

Vancomycin

Vancomycin pharmacokinetics are assumed to conform to a two-compartment open model in Precise PK™ To accomplish the fitting with a fewer number of levels during the distribution phase, K_{21} and Vc are fixed and are not allowed to vary once the original population estimate is made. Parameters that are assigned by the program are as follows: salt fraction = 1 and bioavailability = 100%. The microrate constant K_{21} is fixed by age group as follows:

Constants:

$$K_{21} = 0.46$$

References: 1 (as recalculated in reference 2), 3, 4

K_{10}, α and β are calculated from Vc, Vd_{β} and CL using the formulas in Chapter 3.

Formulas:

Clearance (L/hr):

$$CL(6\ months\ and\ over) = (0.79 \times CLcr + 0.05 \times adjusted\ weight) \times 0.06$$

References: 3-13

$$CL(under\ 6\ months) = 0.006 + total\ body\ weight \times (0.028/Crs + 0.046355 \times age\ in\ yr \times PNA + 0.0123 \times GA)$$

where PNA = 1 if Crs ≤ 0.7 or PNA = 0 if Crs > 0.7
and GA = 0 if the infant's gestational age ≤ 28 weeks and age ≤ 60 days or
GA = 1 if the infant's gestational age >28 weeks

Reference: 19

Volumes of Distribution (L):

Central

Vc (6 months or under) is calculated as follows:

$$Vss = 0.793 \times total\ body\ weight + 0.01$$

$$Vc = 0.666 \times Vss$$

Reference: 19

$$Vc(over\ 6\ months) = 0.17 \times dosing\ weight$$

References: 1 (as recalculated in reference 2), 3, 4, 12-14

$$Vc(adults\ with\ CLcr\ under\ 10\ mL/min) = 0.45 \times dosing\ weight$$

References: 17,19

Total

$$Vd_{\beta}(over\ 6\ months) = 0.7 \times dosing\ weight$$

References: 1 (as recalculated in reference 2), 3, 4, 10-13

$$Vd_{\beta}(adults\ with\ CLcr\ under\ 10\ mL/min) = 1.0 \times dosing\ weight$$

Reference: 17

Vd_{β} (infants 6 months and under) is calculated as follows

$$k_{10} = CL/Vc$$

$$CLq = 0.0334 \times total\ body\ weight$$

$$k_{12} = CLq/Vc$$

$$a_0 = k_{10} \times k_{21}$$

$$a_1 = -(k_{10} + k_{12} + k_{21})$$

$$\beta = \frac{-a_1 - \sqrt{{a_1}^2 - 4 \times a_0}}{2}$$

$$Vd_{\beta} = CL/\beta$$

Reference: 19

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: CL - 50% (32% in infants 6 months and under), Vdβ - 30% (16% in infants 6 months and under), CF - 50%. The time weighting or is 1.005.

Modifying Factors

Critically Ill or ICU Patients. Critically ill and ICU patients have a larger volume of distribution than other patients and their variability over time is greater.[20,21] Vd_{β} is increased by 13% in patients over 1 month of age and time weighting is increased to 1.0.

Burn Patients. Burn patients often have high creatinine and vancomycin clearances, but the relationship between the two is essentially the same as in unburned patients.[3,14,15] Precise PK™ allows creatinine clearance to range as high as 265 mL/min in this patient group and calculates vancomycin clearance as for other patients.

Gestational Age <28 Weeks. Neonates with a gestational age less than 28 weeks have altered vancomycin clearance compared to other infants. These are accounted for in the clearance equation above and applies only to infants 60 days of age or younger.[19]

Patent Ductus Arteriosus (PDA). Limited data (which are consistent with aminoglycoside data) indicate that $Vd_{ß}$ is increased by 47% in infants with patent ductus arteriosus. This effect probably persists for a few days after treatment with indomethacin. This factor applies only to infants less than 30 days old who weigh less than 1 kg.[16]

Reference

1. Schaad UB et al. J Pediatr 1980;96:119-26.
2. Baker D et al. J Pediatr 1980;97:502-3. Letter.
3. Rotschafer JC et al. Antimicrob Agents Chemother 1982;22:391-4.
4. Rodvold KA et al. Antimicrob Agents Chemother 1988;32:848-52.
5. Rodvold KA et al. Ther Drug Monit 1989;11:269-75.
6. Benet LZ, Sheiner LB. In Goodman AG et al, eds. The pharmacological basis of therapeutics, 8th ed. New York. Macmillan 1990:1714.
7. Gross JR et al. Pediatr Pharmacol 1985;5:17-22.
8. Reed MD et al. Pediatr Res 1987;22:360-3.
9. Lisby-Sutch SM et al. Eur J Clin Pharmacol 1988;35:637-42.
10. Krogstad DJ et al. J Clin Pharmacol 1980;20:197-201.
11. Cutler NR et al. Clin Pharmacol Ther 1984;36:803-10.
12. Blouin RA et al. Antimicrob Agents Chemother 1982;21:575-80.
13. Garaud JJ et al. J Antimicrob Chemother 1984;14(suppl D):53-7.
14. Matzke GR et al. Antimicrob Agents Chemother 1984;25:433-7.
15. Brater DC et al. Clin Pharmacol Ther 1986;39:631-4.
16. Spivey JM et al. Am J Dis Child 1986;140:859.
17. Tan CC et al. Ther Drug Monit 1990;12:29-34.
18. Hoie EB et al. Clin Pharm 1990;9:711-5.
19. Capparelli EV et al. J Clin Pharmacol 2001;41:927-34.
20. Llopis-Salvia P et al. J Clin Pharm Ther 2006;31:447-54.
21. Polard E et al. Ther Drug Monit 1999;21:395-403.

APPENDIX A. ANTIBIOTIC PHARMACODYNAMICS

There has been considerable work on the incorporation of microbial sensitivity data together with patient-specific pharmacokinetics in order to optimize antimicrobial therapy. The use of this method of integrating individual patient pharmacokinetics with the MIC of infecting organisms has been termed, "dual individualization". The microbial pharmacodynamic parameter common
to almost all methods is the minimum inhibitory concentration (MIC) of the infecting organism. This is value obtained *in vitro* from bacterial cultures. While not a flawless measure of bacterial sensitivity, it is widely used and reported. Potential pitfalls in the use of the MIC have been reviewed.[1] Since there is not currently general agreement on which (if any) value is the best overall, Precise PK™ calculates the three most widely used pharmacodynamic values. These values, their methods of calculation, and the experience with each are described.

Time Above the MIC

This function is used with antibiotics to calculate the amount of time per day that the serum concentration is above the MIC of the organism being treated. For one-compartment drugs (e.g., aminoglycosides), values used include the clearance (CL), salt fraction (S), bioavailability (F), compliance factor (CF), infusion time (tinf), dose (D), dosage interval (τ) and steady-state trough level (troughss) based on the on the intermittent infusion model,
where K0 = S x F x CF x D / tinf and kd = CL/Vd.
The calculation is made in two phases: an approximation of the time that the serum concentration passes the MIC on the upswing (t_1) is subtracted from the time since the end of the infusion that the serum concentration passes the MIC on the downswing (t_2)[2].
For two-compartment drugs (e.g., vancomycin) an iterative method is used to approximate the time above MIC to the nearest 0.1 hour.

One-Compartment Formulas:

$$t_1 = \frac{MIC - Trough_{ss}}{Peak_{ss} - Trough_{ss}} \times t_{inf}$$

If t_1 is less than 0, t_1 is set to 0

$$t_2 = \frac{\ln\left(Peak_{ss}/MIC\right)}{Kd}$$

Time above $MIC = (t_2 + t_{inf} - t_1) \times 24/\tau$

Post/MIC Ratio

The post/MIC ratio is defined as the ratio of the "peak" serum concentration (drawn up to 1 hour after the end of the infusion) divided by the MIC. The greatest amount of experience with this value has been with the aminoglycoside antibiotics.[4-6] The rate of successful aminoglycoside treatment is improved with values over 6 mg/L.[7] With infections in relatively "protected" or inaccessible sites such as the lung, higher values may prove to be better. Extending these findings, the use of larger doses at longer dosage intervals has been explored. Once daily use of aminoglycosides has been reported and may have equal or greater efficacy and lower toxicity than multiple daily dose regimens.[7]

The time above the MIC appears to be most useful for drugs that act on the bacterial cell wall (e.g., ß-lactams, vancomycin). Maximizing time above the MIC with these antibiotics appears to improve their efficacy when used against susceptible organisms.[1,3]

The concentration of drug in plasma should exceed the MIC for all or most of the 24-hour period daily for optimal efficacy with drugs having little or no post-antibiotic effect against the organism (e.g., ß-lactams against gram-negative organisms). However, this alone may not be sufficient because some resistant organisms may require high peak levels for optimal killing.[1]

AUIC

Several slightly different methods of combining the area under the serum concentration-time curve with the MIC have been reported to correlate with antimicrobial efficacy. The method with the most study in humans is the area under the inhibitory curve (AUIC).[2,8,9]

The AUIC is a value derived by first calculating the area under the serum concentration-time curve (AUC). AUC is then divided by the MIC of the organism to calculate the AUIC value which technically is dimentionless, although the unit "SIT^{-1}" or "inverse serum inhibitory titer" has been applied to this value. It also is suggested that the time above the MIC should be maintained at 24 hours in seriously ill hospitalized patients while applying the AUIC method.

An AUIC value that appears to predict antimicrobial efficacy is 125. This value may apply across antimicrobial classes.[2] Clinically a value of over 125 has been associated with success of ciprofloxacin, although higher values appear to offer more rapid eradication of organisms.[9]

The method of calculating AUC has varied, with most of the work published by Schentag and colleagues using a rather complex method that calculated the area only during that the serum drug concentration exceeds the MIC (i.e., between the times where the serum concentration first exceeds the MIC and first drops below the MIC as in the time above the MIC calculation).[2]

However, more recently, most investigators, including Schentag, have standardized on using simpler calculation of the total AUC below:[10]

AUIC Calculations:

$$AUC = \frac{S \times F \times CF \times Dose}{CL} \qquad AUIC = \frac{AUC \times 24}{MIC \times \tau}$$

Suggested Pharmacodynamic Targets[11]

Antibacterials	Killing characteristics	Pharmacokinetic targets
Aminoglycosides	Concentration dependent	Peak/MIC ratio: 8–10
Beta-lactams	Time dependent	Time above MIC: 40–100% of dosage interval or 40–100% of dosing interval >5 times MIC
Fluoroquinolones time dependent	Concentration &	Post/MIC ratio: 6–8 AUIC (Gram-negatives): 100–125 AUIC *(Streptococcus pneumoniae)*: 34
Linezolid	Concentration dependent	AUIC *(Streptococcus pneumoniae)*: 50 AUIC (*Staphylococcus aureus*): 82
Vancomycin	Concentration dependent	AUIC (*Staphylococcus aureus*): $400

References

1. Dudley MN. Commentary on dual individualization. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics, 3rd ed. Spokane. Applied Therapeutics. 1992:18-1 -13.
2. Schentag JJ et al. DICP Ann Pharmacother 1991;25:1050-7.
3. Schentag JJ. Scand J Infect Dis Suppl; 1991;suppl 74:218-34.
4. Deziel-Evans LM et al. Clin Pharm 1986;5:319-24.
5. Moore RD et al. J Infect Dis 1987;155:93-9.
6. Drusano GL. Antimicrob Agents Chemother 1988;32:289-97.
7. Knoben JE, Anderson PO, eds. Handbook of clinical drug data, 7th ed. Hamilton, Il. Drug Intelligence Publications. 1993:334-7.
8. Schentag JJ et al. Dual individualization with antibiotics: integrated antibiotic management strategies for use in hospitals. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied pharmacokinetics, 3rd ed. Spokane. Applied Therapeutics. 1992:17-1-20.
9. Forrest A et al. Antimicrob Agents Chemother 1993;37:1073-81.
10. Schentag J. Personal communication. December 8, 1993.
11. Choi G et al. Blood Purif. 2010;30:195-212

APPENDIX B. CURVE FITTING

Precise PK™ uses both Bayesian and least-squares curve fitting methods to adjust the population values of pharmacokinetic parameters (F, Vd, CL, CF) as serum level data are obtained. The Bayesian model used was originally described by Sheiner LB et al. Comput Biomed Res 1972;5:441-59 and Clin Pharmacol Ther 1979;26:294-305 and is mathematically expressed as follows:

$$\sum_{i=1}^{N} \frac{(P_i - P_i')}{SD_p^2} + \sum_{j=1}^{M} \frac{(Cp_j - Cp_j')^2}{(SD_{Cpj})^2}$$

where

N = the number of parameters fitted: N = 4 for outpatient oral drugs; N = 3 for inpatient oral drugs; N = 2 for inpatient intravenous and intramuscular drugs. For nonsteady-state phenytoin, N is one greater for each of these situations.

$\overline{P}_i$ = initial (population) estimates for each pharmacokinetic parameter;

P_i = revised (fitted) estimates for each pharmacokinetic parameter;

SD_P^2= variance of the pharmacokinetic parameter;
M = the number of serum levels obtained; M can range from 0 to 9 in Precise PK™;

Cp_j = the serum concentration predicted from initial parameter estimates;

SD_j'= the predicted serum concentrations (based on revised parameter estimates);

$(SD_{Cpj})^2$ = variance of the predicted serum level;

$SD_{Cpj} = (Cp_j' \times SD_e + FE) \times Q^t$ for drugs other than phenytoin. For phenytoin, Vmax, Km and Vd have an $SD = (coefficient\ of\ variation + FE) \times Q^t$.

SD_e = Coefficient of variation of the assay error: Bayes: 0.1 (10%), least squares: 0.01 (1%);

FE = fixed error due to unaccounted for variability such as model misspecification; Bayes: 5%
of the midpoint value of the therapeutic serum level range; least squares: 0

Q^t = time weighting multiplier;With least-squares fitting, the coefficient of variation of the serum levels (SD_e) is changed to
1% and FE is changed to 0 causing population parameters to be virtually eliminated and only
serum level data to be considered in arriving at the final estimate.

Q is a time weighting factor (typically 1.005 or 1.01) and t is the time in hours between the time of the most recent serum level and the time of the serum level t hours previously. The
time-weighting factor applies in both the Bayes and the least-squares fitting routines, except for phenytoin where it is not applied. The effect of the time weighting factor is to cause earlier serum levels to have less "weight" or impact than more recent levels. More recent levels should be a better reflection of the patient's current pharmacokinetic status than older ones. The effect of this factor can be seen on the graphs where early levels sometimes seem to be further from the curve than more recent levels. Drugs whose pharmacokinetic parameters changes more dramatically with time (e.g., because of enzyme induction or disease state alterations) are
time-weighted more heavily. The table below shows the effect of some representative times on the weight of the levels:

Time Weighting Factors

Time of Sample	1.005	1.01
Most recent	1.00	1.00
12 hours prior	0.94	0.89
1 day prior	0.88	0.79
2 days prior	0.79	0.62
3 days prior	0.70	0.49
4 days prior	0.62	0.38
5 days prior	0.55	0.30
10 days prior	0.30	0.09
20 days prior	0.09	0.01